The Lancet · Saturday 5 November 1960

72/3

PROGNOSIS AND NTICOAGULANT PROPHYLAXIS AFTER CORONARY OCCLUSION

J McMichael
M.D Edin., F.R.C.P , Hon F.A.C.P , F.R.S
PROFESSOR OF MEDICINE

E H. O Parry
M.B Cantab , M.R.C.P
MEDICAL REGISTRAR *

DEPARTMENT OF MEDICINE,
POSTGRADUATE MEDICAL SCHOOL, LONDON, W 12

HE outlook after myocardial infarction has usually n assessed by comparing results of treatment in a few e patients with a simultaneous control series The atively small numbers in clinical trials (and in a disorder uch variable course 100 must be regarded as small), lead to chance results which are deceptive. In most he trials unequivocal diagnostic criteria have been anded, and these have usually been the characteristic ures that have been recognised for the past thirty s A positive diagnosis is almost irrefutable, and the errors are those of omission (Paton 1957) The ies of Björck et al. (1958) do not support the idea that nt improvements in finesse of diagnosis have added nts with improved survival prospects Before long- anticoagulant therapy was introduced there were y studies on prognosis, and to neglect them would be obbish ' (Björck 1960)

e begin by reviewing the more important of these w-up studies to reveal the factors on which prognosis depends We are not concerned with the vexed problem of immediate mortality in the acute phase (Morris et al 1952), but with the survival prospects of those who have recovered from a single recognised acute infarction Though we shall mention some studies which deal with first or subsequent infarctions, and some which include angina, these are mainly used to provide supporting data on certain aspects

Wider appreciation of the methods of calculating life-tables has compelled the discarding of many older studies where survival was estimated on patients who had died, and the recalculation of others such as the data of Sigler (1951) who tabulated the dead and living separately Other papers were discarded because of inadequate information on important influences such as age

Factors Influencing Prognosis

The more important studies on prognosis are summarised in tables Ia, Ib, and Ic, and are illustrated in figs 1 and 2 The studies on myocardial infarction total 5398 patients, while the series including angina adds another 8639 While five-year survival tends to cluster round 65–70%, it will be shown that survival is much better in younger patients who have made a good recovery and worsens with increasing age in those with extensive lesions, and with complicating conditions like hypertension and diabetes

Age and Sex

There is a striking difference between survival prospects in Waldron and Constable's (1950) series and those of Eckerström (1951) the average age in the former was 51 5 but the average age (66 7) of the latter series was obviously weighted by a substantial number in the eighth decade or over Inspection of table I shows a general trend to higher five-year mortality

TABLE Ia—PROGNOSIS AFTER SURVIVAL FROM THE FIRST MYOCARDIAL INFARCTION

Author	Patients		Start of follow-up	Percentage survival									
	Number	Mean age		1	2	3	4	5	6	7	8	9	10 (years)
s et al. (1952)	123	54	1 month	96		90		83					
and Marks (1953)	166	51·5	Disability benefit	93	84	81	76	70	67	63	58	54	53
(1953)	85		2 months	88		71		64					53
et al (1954)	285	57	2 months					67					44
(1956)	211	58	2 months	92	84	75	68	60	54	48	44	40	37
der and Levander (1959)	232	57	End of 1st admission					58					
et al. (1960)	427	53	2 months	92	86	79	73	69					
ms et al (1960)	235	62	1 month			69		55					29

TABLE Ib—PROGNOSIS AFTER SURVIVAL FROM FIRST OR SUBSEQUENT INFARCTION

Author	Patients		Start of follow-up	Percentage survival									
	Number	Mean age		1	2	3	4	5	6	7	8	9	10 (years)
tröm (1951)	109	66 7	1 month	67	51	41	36	30					
on and Constable (1950)	1551	53	3 months	91	84			69					55
et al. (1956)	126	63	2 months	84				54					18
rds et al. (1956)	162	56 7	1 month					49					31
und and Hougen (1956)	929	63 1	1 month	80	60	55							
y and Truelove (1957)	348	59	2 months	86	76	70	65	61	53	41	38	32	32
k et al. (1958)	246	63	End of 1st admission	83	76	69	63	59		50			40

TABLE IC—PROGNOSIS IN PATIENTS WITH ANGINA PECTORIS OR INFARCTION

uthor	Patients		Type	Start of follow-up	Percentage survival					
	Number	Mean age			1	2	3	4	5	10 (years)
(1951)	1147	55 8	Angina and infarction	Diagnosis	91	86	82	79	77	
et al. (1952)	6882	55 8	Angina and infarction	2 years after diagnosis	84		70		58	37
(1960)	610	59·6	Angina	Diagnosis of angina	92	88	83	79	74	

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* ent address Department of Medicine University College Hospital, adan Nigeria

TABLE II—CAUSES OF DEATH

Author	Total deaths in series	Causes of death—as percentage of total in each series				
		Recurrent infarction	Sudden death	Congestive heart-failure	Cerebrovascular accident	Other
Levine and Rosenbaum (1941)	80	40	35	20		5
Katz et al (1949)	52	65 4		19 2		15 4
Sigler (1951)	393	56	14	13	5	12
Cole et al (1954)	171	55		17	7	21
Olsen et al (1956)	87	31	17 5	20 5		31
Richards et al (1956)	160	51*		25		24
Weiss (1956)	142	38 7	19	23 3	7	12
Honey and Truelove (1957)	107	45		33 5		21 5
Bjorck et al (1958)	489	42		32†	7	19
Juergens et al (1960)	82	34	27	21	7	11
Seim (1960)	372	26	15	23	13	23

* This figure applies to cases described as "coronary insufficiency"

† This figure applies to all cases of coronary heart-disease without evidence of acute infarction

These studies show that the chances of survival following acute infarction can be assessed by consideration of *age, sex, economic status, severity of the attack* and degree of recovery, and complicating diabetes or hypertension The slightest degree of unintentional bias in the selection of patients for treatment and control groups could profoundly influence the results

Anticoagulant Treatment

The use of dicoumarol and phenindione in the treatment of acute myocardial infarction has been followed by a significantly lower mortality during the acute phase Wright et al (1948) reported the results of the American Heart Association's trial which showed a 24% mortality in the control series compared with a 15% mortality in the treated In patients under 60 the crude death-rates were the same in both groups, but there was less nonfatal thromboembolism in the treated patients They accordingly advocated the use of anticoagulants in the acute phase, especially in patients aged 60 and over Feldman et al (1952) studied 189 patients, and did not find that mortality was reduced, or that thromboemboli were less frequent in a series of treated and control patients matched for age, sex, and cardiovascular status The work of Gilchrist and others in this country (Gilchrist and Tulloch 1956) has established a place for anticoagulant treatment in the acute phase, particularly to reduce thrombosis on the venous side, and subsequent emboli in the pulmonary and systemic circulations That these are the effects of anticoagulants is postulated by Bjerkelund (1957), but he cautiously states that "one is hardly justified in concluding that this form of treatment also prevents arterial thrombosis, including coronary thrombosis itself, which in many respects is thought to be of a different nature and related to other pathogenetic factors"

The claims of improvement in prognosis from acute-phase treatment have led to widespread interest in long-term treatment, but, in the absence of critical and controlled work, it is difficult to define the place of anticoagulants in preventing myocardial infarction Gilchrist (1960) admits that in our present experience, and in the absence of all the desirable evidence, the case for long-term anticoagulant therapy amongst those with permanent myocardial damage is "not proven", though the evidence in favour is very suggestive Writing before the Medical Research Council (M R C) (1959) report was published, Jordan and Punt (1958) suggested that "a study of the publications shows that—although the results are generally described as favourable—it is exceedingly difficult to use the figures given as a basis for a definite conclusion regarding this therapy"

Control Series

We have shown that the prognosis for survival after recovery from myocardial infarction is influenced by many factors affecting the results of any trial unless critically matched in control and treated groups Sometimes published results appear convincing until the control group is analysed Bjerkelund (1957) and the M R C (1959) studied patients who were matched accurately, but most other papers are less reliable

Lack of an Adequate Control Group

Keyes et al (1956) showed that mortality of their treated patients was 8 4% in four years compared with 41% in the same period in the untreated with first infarctions No facts are given about the age, sex, or history of either the control or treated group, the former being two-and-a-half times as large as the group of 71 trated patients, suggesting some selection

Tulloch and Wright (1954) studied a very small group (32 patients after the late phase of myocardial infarction) with a fifteen-month mortality of 6 2%, but they gave no facts about their patients, and so it is impossible to assess the results, and, in any case, this mortality does not differ significantly from the upper range of large untreated series (fig 8)

Ensor and Peters (1959) used a "pseudo-control" group—i e, a group of patients who had had anticoagulants for some time but who had discontinued treatment The only fact given about the patients is the severity of the myocardial infarction in the treated group, but these authors are cautious in their claims as they only report a 79% five-year survival in treated patients against 70 7% in the "pseudo-controls"

Nichol et al (1958) studied the effect of anticoagulant treatment in patients with impending infarction, or in

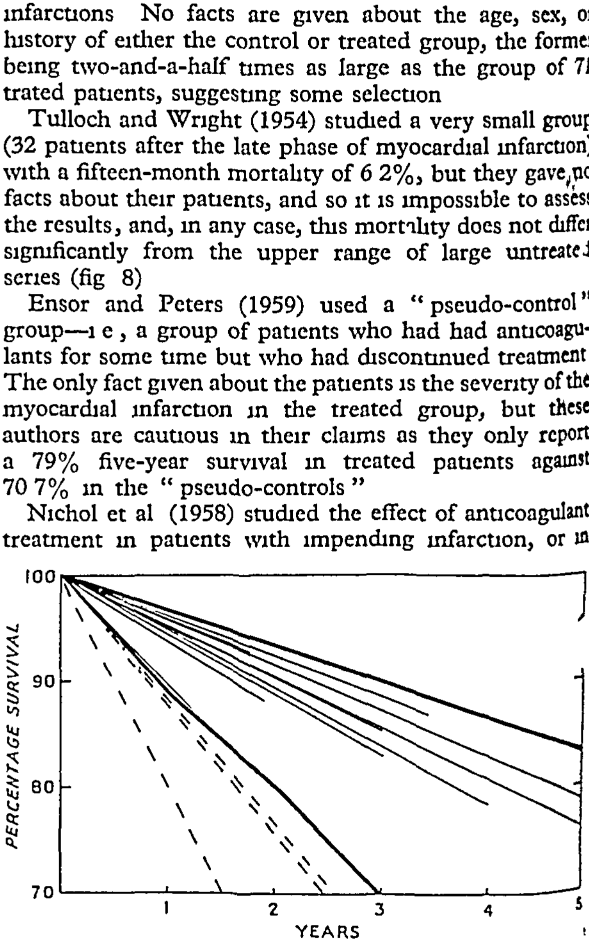

Fig 8—Treated series compared with untreated

The general prognosis derived from fig 1 lies between the thick lines The survival of treated patients (continuous lines) is shown using survival table data or percentage survival at the end of the average length of treatment The treated series from above down are (1) Tandowsky (1959), (2) Muri (1956), (3) Ensor and Peters (1959), (4) Suzman (1959), (5) Ødegaard (1958), (6) Tulloch and Wright (1954), (7) Bjerkelund* (1957), (8) Waaler† (1957), (9) Nichol et al (1958), and (10) Nichol and Bork (1950) The controls (dot-dash lines) from above down are those of Nichol et al (1958), Bjerkelund (1957), and Suzman (1959) While the treated series tends slightly into the upper range of survival, the controls fare worse than usual

* Based on total deaths † Includes patients with angina

with one or two previous infarctions They used controls, however, patients from their records who been previously followed up without any treatment ney also named a group of patients who abandoned -term treatment It is significant to note that 14% the deaths in this group occurred within one month stopping anticoagulants But none of the groups matched and the average period of follow-up in each Their treated patients showed an 88% vival after an average period of 1 87 years, well within ns of past experience (fig 8)

Suzman et al (1955) present formidable figures to that patients on long-term treatment do better than treated during the acute phase only Although this a careful study, the chief drawback to their results is " the final decision for long-term treatment was left the patient " Economic factors obviously entered into selection, and the results of treatment were a five-year val of 76 1% against 45 6% in the untreated cases uzman (1959) has kindly allowed us to see his unpub- figures which show that recurrent infarction ccurred only slightly less often (34 7% against 43 2%), its mortality was less (40 5% against 74 8%) in long- treatment patients than in the short-term group results, however, must be seen against the background of the selection of patients and the age-distribution of the groups, 31% of the patients in the short-term group were over 70, compared with only 20% in the -term group

Tandowsky (1959) does not mention his patients' status, except to describe the 70 controls as " a like group " in whom the mortality (53%) was four times that of the treated (13%), the average duration of treatment was three years and five months

Use of Retrospective Studies to Provide Control Groups

Some papers which have given encouraging figures for urvival in patients treated with long-term anticoagulants not had a concurrent control series Some writers have compared a series of patients treated in one country ith a series reported in a different country some years efore. Thus, Muri (1956) who had a 7 5% mortality an average exposure to risk of twenty-one months ompared his results with those of Parker et al (1946) which were later included in the total series of Block et al 1952), both reporting an exceptionally high (19 and 16% espectively) first-year mortality Waaler (1957) who chieved a 17% three-year mortality, also used as controls he data of Block which are seen to be much worse than hose of Sigler or Seim (table IC)

Tanzi and van Ness (1957) compared their mortality f 6 1%, in a sixteen-month average, with those " so far eported " Toohey (1958), who had an 11 6% mortality t eighteen months, used as controls patients who had een followed up after myocardial infarction in the same nd another hospital during the seven years before long- erm anticoagulants this series had a 33% two-year mortality Toohey did not mention either age or sex mong his patients, and so it is not easy to accept the laim that his results are " statistically significant " His ontrols, who had a much higher mortality than usual, ay have been an aged group, and his treated patients ere not matched with the controls in any way

dmission to Treated Group and Follow-up Care

Tanzi and van Ness (1957) and Keyes et al (1956) mited their treatment to those who could cooperate The former achieved 6 1% mortality in sixteen months while the latter had a 9 9% mortality between one and thirty-eight months of observation, results which lie within upper range of life expectation as shown in fig 1 The striking five-year survival, 83%, which Morris et al (1952) reported in medical practitioners, demonstrates the part played by intelligence, social status, and careful follow-up in survival after myocardial infarction Constant supervision is certain to ensure earlier treatment of symptoms which may arise, and this is the only way in which the control group of patients in Bjerkelund's (1957) admirable study differed from the treated group The latter were seen every one to three weeks against the three to four monthly intervals between the visits of control patients

Results of Treatment

Although many reports have an inadequate control series, they give valuable facts about survival in the treated patients

Survival of Patients

Many of the earlier papers included a few patients with myocardial infarction, and a larger series treated with long-term anticoagulants for thromboembolic disease, and so are not satisfactory for survival data Tulloch and Wright's (1954) and Muri's (1956) figures have already been discussed Nichol and Borg (1950) treated 78 patients for an average of fifteen months and reported a 15 3% mortality, which is less good than the average (fig 8) Ødegaard (1958) treated 117 patients, of mean age 58 9 for a total of 343 patient-years, and found a mortality-rate of 4 87% per year—a little better than average but not outside the range of untreated patients There was a 10% mortality in 735 patients with one infarction, studied for an average of twenty months by Nichol et al (1958) they also reported an overall mortality rate of 12% in 1091 patients with impending one or two infarctions, studied for an average of 22 4 months Both these figures are within " untreated " expectation Manchester (1957) expresses his results as the fatality, and number of recurrent infarctions per 100 patient-years, these figures were 0 56 and 2 73 respectively A survival table cannot be made from his data He had twice as many patients with heart-failure requiring digitalis (33%) in his control group as in his treated group (15 6%) The five-year survival of 76% in Suzman's (1959) treated patients may well reflect the better social status of his patients

The chief interest in the reports of Bjerkelund (1957) and the M R C (1959) is the difference which is shown between the control and treated patients during the early months of long-term treatment Bjerkelund (1957) stated that the " force of mortality " seemed to be largest initially in the control group, and that the treated patients—but only those under 60—did not show this initial excess mortality It is noteworthy that in both Bjerkelund's and the M R C series, most of the excess deaths in the controls took place in the first three months after infarction Bjerkelund reported no statistical difference between the " force of mortality " in the treated and control group at any age, a year and more after infarction (see figs 5 and 6 of his monograph) The M R C trial showed a similar trend, and although 19 of the 28 deaths in the low-dosage group occurred in the first six months compared with only 9 of the 17 deaths in the high-dosage group " the difference in the death rate was appreciable only during the first three months of the follow-up period " These results are best demonstrated by the death-rates per 100 man-months of exposure during the first year

Period	*Low dosage*	*High dosage*
Less than 3 months	2 7	0 8
3-6 months	1 7	1 1
6-9 months	0 8	0 5
9-12 months	0 0	0 8

While both these reliable reports show similar results, the efficacy of anticoagulant drugs was only transient Suzman (1959) and Manchester (1957), however, report sustained improvement of prognosis, and so these four important protagonists are far from agreement on the reasons for their advocacy of long-term treatment

No reported series shows that anticoagulant treatment in any way affects the pattern of an increasing mortality with age, or benefits older patients This is thoroughly borne out by Bjerkelund's (1957) results with his older (over 60) patients, whom treatment did not benefit Similarly, the difference between the low-dosago and high-dosage groups of men aged 55 and over was less marked than that in men under 55, which itself did not reach the 5% level of significance (M R C 1959)

These results, and those which have been given above, show that it is probably only in the acute and healing phases of myocardial infarction that anticoagulant treatment may be effective in increasing survival, but even this is not yet statistically proven Long-term anticoagulant prophylaxis beyond about two months after infarction cannot yet be justified by adequate evidence

In small numbers of patients—and we must count the M R C and Bjerkelund series as small—there are obviously possibilities of great variability indicated by "highly significant" results diminishing with the passage of time to statistical "insignificance" in both series That chance could readily operate to account for the results is borne out by the recent work of MacMillan et al (1960) In a statistically randomised series of 27 treated and 23 untreated patients, they had 8 deaths in the treated as against none in the untreated "controls"

Recurrence of Infarction During Treatment

The difficulties of establishing this diagnosis have already been mentioned, and the papers which report the results of treatment are not precise in defining the criteria for a recurrence Bjerkelund (1957) alone classifies his patients into those with definite, very probable, and probable recurrences, and he points out that the diagnosis could not be established with equal certainty in all cases However, the diagnosis of his recorded instances was definite in 63 5% of treated, and in 76% of untreated patients He is careful to state that cases of sudden death were only included as recurrent infarcts if definite signs of a fresh infarct were found post mortem Thus, his criteria differ from those of the M R C report (1959) in which all cases of sudden death were attributed to recurrent infarction Manchester (1957) does not mention the criteria for recognising a recurrence These divergences explain the varying results of table III, where the incidence and mortality of recurrences in treated patients are shown. The apparent tendency towards a lower rate of reinfarction in the treated patients is open to critical doubt on account of the above difficulties of controls and diagnosis.

Certain facts must be emphasised which arise from this study of reinfarction Bjerkelund (1957) makes a thorough study of the "force of recurrence" in his control group and shows a definite "excess of recurrences" in those under 60 during the first six months—but shows that this is not significant in the patients more than 60 years old Moreover, after twelve months he can find no statistical difference between the "force of recurrence in the treated and control groups, and he finds that anticoagulant therapy has not given much protection to those with a high "force of recurrence"—i e , those with a previous recurrent infarction He claims that during the observation period two-fifths of the recurrent infarctions and at least half of the deaths due to recurrences were prevented by dicoumarol treatment His most significant differences, however, were either in the first month of observation (i e , near the acute phase) or in patients over 70

The M R C (1959) data on recurrent infarction differ from those of Bjerkelund in suggesting that a disparity in infarct-rate between high-dose and low-dose patients continues into the second year of follow-up Although there were fewer cases of recurrent infarction among the treated, 17 out of 24 died from their recurrence, against 29 out of 60 in the low-dose group

A reduced incidence of recurrent infarction in treated patients was also reported by Manchester (1957) and his results appear to be formidable evidence, but he did not give details of the patients studied, nor any criteria for the diagnosis of a recurrence A large number (157) of his patients abandoned treatment, and these may have weighted survival in those continuing treatment towards a better prognosis, with fewer recurrences, as the M R C report suggests

Suzman (table III) also found a slightly lower rate of reinfarction in his long-term treated patients, especially in those whose previous infarction had been severe However, the mortality of recurrent infarction was higher in the control group (49 4% against 27 6%) It is noteworthy that the mortality in Suzman's "treated" recurrences was about half that in the M R C series where it was remarkably high (75%) Bjerkelund (1957) found that patients with a mild previous infarction had fewer recurrences, whereas Suzman (table III) found the reverse Recommendation of long-term anticoagulants is thus based on widely divergent findings

TABLE III—RECURRENT INFARCTION IN TRIALS OF TREATMENT

Author	Number of patients		Period of study (years)	Recurrence of infarction			
				Control		Treated	
	Control	Treated		Incidence (%)	Mortality (%)	Incidence (%)	Mortality (%)
Keyes et al (1956)	231	121	2	38 0		2 0	
Bjerkelund (1957)	118	119	3	40 (*a*)	41 6	22 (*a*)	34 6
Manchester (1957)	200	204	10	31	53 0	14 2	20 6
Nichol et al (1958)		1091	1 87			10 75 (*b*)	66
Medical Research Council (1959)	188	195	3	27 5	46 5	12 3	75
Suzman (1959)	216 (*c*) mild	55	10	32 8	19 4	34 5	27 6
	298 (*c*) severe	115	10	50 7	61 4	31 8	38 3

(*a*) Includes cases classified as definite, very probable, and probable myocardial infarction
(*b*) Includes cases described as ventricular fibrillation or cardiac arrest (i e , sudden death)
(*c*) Refers to severity of first attack of infarction

to Work

It has already been shown that many patients are able return to work, and to stay at work after recovery myocardial infarction without long-term treatment. is disappointing, therefore, that Bjerkelund (1957) d that only slightly more treated than control patients d to work. The small difference between the two ups probably depended upon more elderly patients mong the controls Bjerkelund states that the "difference hardly gives reason to believe that the treatment has uced the patient's ability to work" The M R C 1959) found that there were slightly more men at work n the treated group (83% against 71%), but the proportion without dyspnœa was the same (66% and 67%) This s the more remarkable as the 31 of the "untreated" vivors had had an additional recurrent infarction Muir (1956) reported that 79% of treated patients were work, a figure in agreement with the M.R C treated and untreated groups, and thus hardly to be claimed as a erapeutic success

A patient's return to work will in part be determined by his symptoms A common symptom which can limit his return to work is cardiac pain, which has been reported be less frequent in patients treated with anticoagulants We wish, however, to repeat Bjerkelund's (1957) statement that "cases of angina pectoris often have spontaneous fluctuations, and this makes assessment of prophylactic therapy very difficult"

Manchester (1957) found that 38 of 74 treated patients had less cardiac pain, compared with only 20 of 72 control patients imilar figures were given by Tandowsky (1959) for the abatement of coronary insufficiency, and Waaler (1957) found that 8% of his series of treated patients with angina pectoris were wholly relieved, and 12% were partially relieved of pain. The M.R.C (1959) reported that the absence of anginal pain uggested a slight superiority among the treated (64% against ?%) over three years of study Bjerkelund (1957) meticulously ubdivided his patients according to their grade of cardiac , but was not convinced that dicoumarol had any "definite" prophylactic effect against this symptom.

Thromboembolism

The prevention of venous thromboembolism after the nitial acute phase does not receive much prominence in ny report, and it is evident that it is not very important linically after the acute phase, though when it is recognised, the mortality is high

Manchester (1957) reported 35 cases (17 5%) of whom 16 45 7%) died in his untreated group, against only 5 8% with 14 2% mortality in his treated patients Bjerkelund (1957) ound extracardiac thromboemboli in only 2 of his control group, and in none of his treated group Suzman (1959) ound thromboembolism three times more frequently in his ntreated patients Only 1 case is mentioned with a fatal cerebral embolus in the M.R.C low-dosage group It seems ikely that patients on anticoagulants are protected from venous hromboembolism (Sevitt and Gallagher 1959)

There is adequate postmortem evidence, however, that oronary arterial thrombosis can, and frequently does, levelop in patients under expert anticoagulant control Fresh coronary-artery thrombosis was found at necropsy n 58% of Bjerkelund's untreated patients, and, post nortem, in 26% of his treated patients Capeci and Levy 1959) were not impressed by any diminution of thrombus ormation in treated patients who came to necropsy

ndications for Treatment

Two different opinions are held about choice of patients or, and duration of, treatment Nichol and Fasset 1947) decided to use anticoagulants for patients with recurrent infarction Wright et al (1954) and Suzman et al (1955) also reported that this type of patient might benefit from treatment The M.R C (1959) found that a lowering of the infarction-rate appeared most clearly in those in whom the risk of recurrent infarction was high, in younger males, and in those with more than one infarct On the other hand, Bjerkelund's results indicated that there was no benefit from treatment in patients who had had more than one infarct he would recommend treating all, or a large number of, patients for six months or a year, but not thereafter The M R C report, however, recommends that "continuous" treatment should be given as this can make a useful if limited, contribution in the aftercare of patients who have recovered from the acute phase of myocardial infarction, in spite of their own evidence that the regime is of little value after six months

Discussion

At the beginning of this paper, we showed that patients who survive the acute phase of a myocardial infarction have a five-year survival-rate of about 66% This figure has varied according to the type of patient who has been followed up, ranging from above 80% in the doctors studied by Morris et al (1952) to 30% in Eckerstrom's (1951) elderly patients We have mentioned the remarkably good five-year survival figures for patients who make a complete clinical recovery, or who are young at the time of their infarction All this evidence shows that myocardial infarction may often be followed by long survival The various factors which affect prognosis have been documented in order to give a background of experience against which the results of long-term prophylaxis may be reviewed

In studying the published reports on anticoagulant prophylaxis, we have become critical of the controls, who have often been at, or below, the lower extreme of prognosis found in untreated patients, while the treated fare no better than those in the upper range of survival prospect (fig 8) The careful studies of Bjerkelund (1957) and of the M.R C (1959) have been a constant source of valuable data, but there is surprisingly little work of similar calibre in other studies

Despite many claims, the evidence that long-term anticoagulants prevent recurrence, or reduce mortality, after the acute phase of infarction is still inadequate Most of the benefits reported by Bjerkelund and by the M.R C working party occurred in the first few months —i e, while patients were still recovering from the acute event If the action of the drugs is to prevent arterial thrombosis, there is no reason why this prophylactic action should cease after a few months, and it may well be that the early benefits reported in the Bjerkelund and M.R C series are in fact related in some way to the early healing phase of the actual infarction Another possibility is of harm to the controls from sudden termination of acute-phase treatment.

It seems possible that most of the benefits which have been reported in the acute phase of infarction are related to the efficacy of the drug in limiting venous thrombosis and preventing pulmonary embolism, most reports are consistent in this respect. The recent studies by Sevitt and Gallagher (1959) on prophylaxis of venous thrombosis with phenindione in patients with fractured femora are most encouraging The apparent failure of the same measures to prevent coronary occlusion is all the more disappointing Antiprothrombin drugs have also failed in cerebrovascular occlusive disease (Marshall and Shaw

1960), and in occlusive arterial disease of the legs (Singer and Rob 1960)

Venous and arterial thromboses probably differ considerably in their pathogenesis Venous thrombosis is undoubtedly promoted by stagnation in veins of the calf, often subjected to prolonged mechanical pressure in bed in debilitated patients Arterial thrombosis, on the other hand, is based on underlying disease of the arterial wall—atheromatous plaques and ulcers, which can liberate local tissue thromboplastins into the blood-stream, which in turn may be retarded by upstream narrowing of the vessel Ischæmia and myocardial infarction have been reported in patients with hæmophilia (Boivin 1954, Borchgrevink 1959, Stewart and Acheson 1957) The development of arterial occlusions in these patients reinforces the importance of local release of thromboplastin from the damaged intima as a crucial event in the changes leading to thrombosis, even of hæmophilic blood (Astrup et al 1959) Mural thrombi over infarcts form with almost equal frequency in patients on anticoagulants as compared with controls (Gilchrist and Tulloch 1956) Such observations raise serious doubts on the usefulness of anticoagulants in preventing local thrombosis on damaged arterial intima

Any problematic benefit from anticoagulants in the prevention of thrombosis should be weighed against the considerable risk of hæmorrhage mentioned in most reports Lethal cerebral hæmorrhage occurred in 4 out of 118 patients in Bjerkelund's (1957) series, 2, and possibly 3, fatalities were also recorded from Newcastle (Fuller 1959) Quite apart from the risk of cerebral and other fatal hæmorrhages, morbidity can result from serious bleeding from anticoagulant treatment Anticoagulants may not avert arterial occlusion, and there is a real, and probably increased, risk of thrombosis in the period immediately after the drugs are stopped Various reports have suggested that sudden cessation of antiprothrombin drugs may be followed by arterial occlusion within a short time (Nichol et al 1958), 20 such instances are documented by Dinon and Vander Veer (1960) It is not impossible that this complication may have been responsible for the early high mortality, so near the end of acute-phase treatment, in both the M R C and the Bjerkelund control patients Hence, when anticoagulants have been used in the acute phase of myocardial infarction, their administration should be tapered off over a period of three to four weeks

Finally, it is well to remember that factors other than thrombosis also play a part in the production of myocardial infarction Among them are thickening of the atheromatous plaques themselves, subintimal hæmorrhage (Paterson 1936, Paterson et al 1957), and sudden falls of blood-pressure reducing perfusion of critically narrowed coronary vessels Furthermore, recurrent thrombosis may be responsible for a little more than half the ultimate death-rate in patients who have recovered from a cardiac infarction

Summary

The survival of patients after recovery from myocardial infarction, and the factors which influence prognosis, have been studied from reported series

There is broad agreement in the published data, totalling over 5000 patients (table 1a and 1b), that the prospect of five-year survival in cases under 60 ranges round 66%, being worse with increasing age and complications, and better with improving social circumstances and completeness of recovery

Long-term anticoagulant prophylaxis, as carried today, shows no evidence of improving life when compared with the prognosis in this large of " untreated " patients

Possible reasons for this inefficacy of long-term an coagulant prophylaxis are briefly discussed against background of contrasting mechanisms of arterial venous thrombosis The possibility should also be considered that some of the early high mortality in " controls may be the result of sudden cessation of " treatment "

We are particularly grateful to Dr M M Suzman and Dr MacMillan for putting their unpublished data at our disposal

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POTASSIUM IN THE TREATMENT OF CHOLERA

RAYMOND H WATTEN
B.A , M D Stanford
ROBERT A PHILLIPS
M.B E , M D Washington, St Louis, B S Iowa
MEDICAL OFFICERS, UNITED STATES NAVAL MEDICAL RESEARCH UNIT NO 2, TAIPEI, TAIWAN (FORMOSA)

Sir Leonard Rogers, in 1909, advocated the use of a ypertonic solution containing sodium chloride, calcium chloride, and 0 4 g (5 4 mEq) per litre of potassium chloride, for the treatment of cholera, but in 1916 he decided to omit potassium from the mixture because 'some physiologists consider it unnecessary and possibly harmful" In 1946, Govan and Darrow demonstrated a fivefold reduction in mortality from infantile diarrhœa when potassium was added to replacement solutions used parenterally Electrolyte studies by the United States Navy in the 1947 Egyptian cholera epidemic showed an excessive loss of potassium in the stools, hence it was recommended that potassium 6 7 mEq be included in each litre of intravenous solution used in the treatment of cholera (Johnson et al 1948) Chakravarti and Chaudhuri, in 1954, recommended giving potassium salts, when the acute diarrhœa of cholera had subsided, to hasten convalescence, providing that renal function was satisfactory Despite the above, a recent review of cholera therapy (Pollitzer 1957) does not mention the use of potassium in the treatment of the acute disease

The Study

During the 1958 cholera epidemic in Bangkok Thailand, eventeen patients with proven cholera were studied intensively during their acute illness For the first 24 hours nothing was allowed by mouth in order to relate the fæcal changes to changes in plasma-electrolyte composition Thus, during the first 24 hours, fluids were given exclusively by the intravenous route. Meanwhile balance studies were made, and afterwards a diet of boiled eggs, rice gruel, milk, and water was given ad libitum The fæces and urine were collected and measured daily until the patient was discharged. A detailed report of his investigation, including methods and procedures, has been published (Watten et al 1959) While it is impossible from hese studies to calculate balance data for more than 24 hours fter admission, approximate potassium losses during the 2–4 days of diarrhœa may be calculated

TABLE I—MEAN HOURLY FÆCAL VOLUME AND ELECTROLYTE CONCENTRATION OF CHOLERA STOOLS COLLECTED OVER 24-HOURS

—	Volume (ml. per hr)		Electrolytes (mEq per l)			
	Mean	Range	Na	Cl	K	HCO_3
11 patients with fæcal volume over 125 ml. per hr	340	130–730	137	107	16 1	45 2
patients with fæcal volume under 125 ml. per hr	100	23–120	114	89	26 4	43 5

Patients with severe cholera had 24-hour fæcal volumes of –17 litres In these patients the total volume of diarrhœal uid during the 2–4 days of the disease was 10–35 litres During the 24-hour balance period, the mean potassium ontent of the fæces was 16 mEq per litre (table I), and otassium losses in fæces and urine averaged 158 mEq , with range of 50–245 mEq The total fæcal and urinary loss of otassium for the entire period of diarrhœa varied from 400 to 700 mEq , or, for a 50 kg man, the loss was 15–30% of the total exchangeable body-potassium, assuming this value to be 9 mEq per kg body-weight for a normal man (Edelman and eibman 1959)

Fæcal potassium concentrations vary inversely with fæcal volume (Watten et al 1959) Table I shows that patients with fæcal volumes in excess of 3 litres per day (125 ml per hour), had fæcal sodium and chloride concentrations which were nearly isotonic with those of the plasma, while the potassium and bicarbonate concentrations were higher than the plasma levels

With amelioration of diarrhœa and decrease in fæcal volume, the potassium concentration increased while the sodium concentration decreased, this is related to selective reabsorption of sodium in exchange for potassium in the lower ileum and large bowel, and it has been demonstrated experimentally by D'Agostino et al (1953) Paralytic ileus, with abdominal swelling and cessation of diarrhœa, was often seen in patients whom we studied during the 1958 Bangkok cholera epidemic

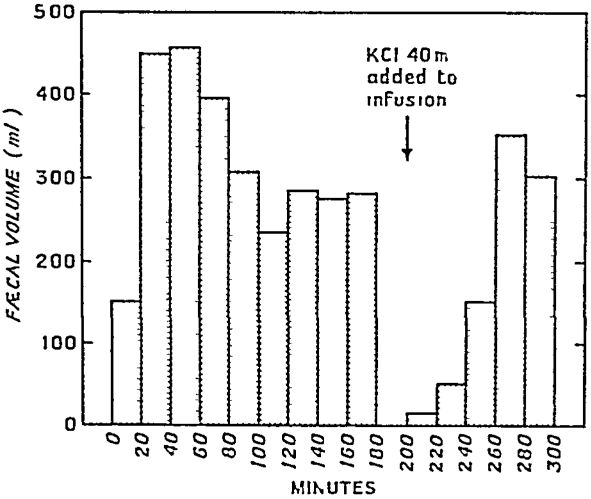

Fig 1—Fæcal volume measured at 20-min intervals during constant infusion (15 ml per min) of normal saline (4-140 min) and 2% sodium bicarbonate (140-240 min)

This complication, as Wilkinson (1943) pointed out, is probably responsible for the rare examples of so-called cholera sicca, in which death results from massive transfer of fluid into the bowel lumen without diarrhœa

Fig 1 shows 20-minute fæcal volumes in a patient during infusions of normal saline and 2% bicarbonate solution The drop in fæcal volume at 180 minutes was probably the result of potassium deficiency, because balances at that time revealed a loss of 165 mEq of potassium Fæcal volume increased after infusion of 40 mEq of potassium chloride, and then it remained constant with additional infusions of potassium The sequestration of a large volume of diarrhœal fluid in the bowel, caused by paralytic ileus, can be misleading and dangerous if fluid therapy is based on replacement of observed fæcal volume alone Utilisation of more accurate measurements of dehydration, such as plasma-specific-gravity determinations (Phillips et al 1950) will prevent such errors

During our cholera studies, alkalosis developed after treatment in four patients who had been given only 20–80 mEq of potassium (replacing about 10% of the deficit) during treatment (table II) The plasma-CO_2 content remained above 30 mEq per litre for as long as 7 days after the diarrhœa

TABLE II—ADMISSION AND CONVALESCENT PLASMA-CO CONTENT AND POTASSIUM LEVELS IN FOUR PATIENTS WITH SEVERE CHOLERA

Patient no	24-hr fæcal volume (ml per hr)	Plasma CO content (mEq per L plasma-water)		Plasma-potassium (mEq per l plasma-water)		Interval (days)
		Admission	Con-valescent	Admission	Con-valescent	
2	476	22 2	29 3	4 5	3 8	7
10	235	14 0	37 0	4 8	3 3	6
12	302	11 1	30 4	4 3	3 1	3
15	725	20 5	33 3	4 9	3 4	7

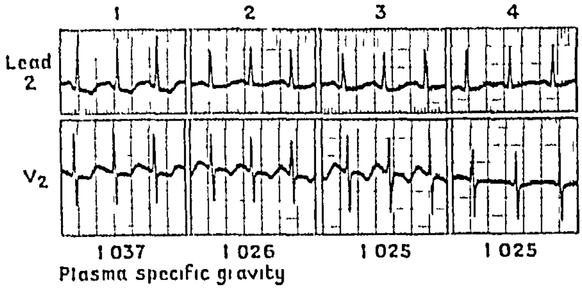

Fig 2—Patient no 6, 30 year-old Thai woman, 24-hour fæcal volume 7700 ml

The tracings were made (1) on admission at 12 30 A M (plasma-CO_2 content 15 mEq per litre), (2) at 2 P M after rehydration with 3 litres of normal saline, (3) at 4 30 P M after infusion of 500 ml of 2% sodium bicarbonate solution (which raised the plasma-CO_2 content to 22 mEq per litre, and (4) at 5 30 P M after infusion of 10 mEq of potassium chloride in 1 litre of normal saline

ceased, despite a normal diet The data were not complete enough to indicate the pathogenesis of alkalosis associated with potassium deficiency in cholera, but they do indicate that a moderate alkalosis developed in several patients with serious potassium depletion, who had been treated with adequate quantities of saline and bicarbonate

Serial electrocardiograms were taken during treatment of thirteen patients, but only five showed definite evidence of potassium deficiency either before or after the dehydration had been corrected with saline Fig 2 shows the changes in a patient with severe cholera During the 5 hours before admission this patient passed seven watery stools, and was moderately dehydrated The first tracing, taken 6 hours after the onset of the patient's diarrhœa, showed T-wave alterations in all leads T-wave changes were less pronounced after saline and bicarbonate infusions, but they did not return to normal until potassium had been given These changes were not caused by dehydration because plasma-specific-gravity values were within the normal range during the infusion therapy

Discussion

Rational treatment of cholera requires knowledge of the altered physiology and chemistry of this disease Such information has not been available until recently (Watten et al 1959), and consequently therapeutic regimens have changed little since Rogers' recommendations of 50 years ago There is universal agreement on the necessity for prompt replacement of water and salt, and the use of bicarbonate for the treatment of acidosis is accepted, but the risk of pulmonary œdema from overhydration (Chaudhuri 1950, Chakravarti and Chaudhuri 1954) is emphasised far more often than the danger of insufficient fluid replacement Myocardial depression caused by potassium depletion rather than by rapid replacement of fluid may well be the important factor in the genesis of this complication Death from "heart-failure" during convalescence (Baligh 1948) may also be due to deficit of potassium Moreover, adjuvants to therapy (colloid plasma-volume expanders, cardiac stimulants, vasopressor agents, bacteriophage, antibiotics, &c) continue to be given emphasis out of proportion to their value, and they detract from what should be the main line of cholera therapy—i e , replacement of the lost water and electrolytes

A lesser-known result of potassium depletion is renal tubular damage, vacuolisation of distal tubular cells, and damage to the collecting tubules, have been reported (Relman and Schwartz 1958, Holliday 1959) In a recent study of patients dying in uræmia after cholera, Benyajati et al (1960) found microscopic changes in renal structure similar to those produced by potassium depletion Ischæmic renal damage and uræmia due to delayed or inadequate fluid replacement is a frequent complication of cholera Damage to kidney structure and impairment of function produced by potassium loss may contribute to renal failure in these cases

Neuromuscular disturbances are a well-known complication of potassium deficiency But there is only one report of transient potassium-depletion paralysis following cholera in eleven convalescent patients, this promptly subsided after potassium-chloride infusions had been given (Huang and Mao 1947) Instances are known of "secondary collapse" involving weakness, muscular twitching, and tetany during convalescence from cholera (Dr C Benyajati, personal communication)

Although plasma-potassium levels will eventually reflect potassium deficits, determinations made during the acute phase of cholera are of no value in establishing the need for potassium replacement Data from our studies (Watten et al 1957) indicate that plasma-potassium levels in acutely dehydrated patients were within the range of normal when corrected for plasma-protein concentration (expressed as mEq per litre plasma-water) Furthermore, plasma-potassium values after rehydration were also within the range of normal These findings indicate, as Scribner et al (1958) concluded, that plasma-potassium concentration is independent of the volume of the extracellular space

Saline solutions have been the foundation of cholera treatment Table I shows that, for each litre of fæces lost from a patient with severe cholera, a litre of approximately isotonic saline will replace the salt lost Theoretically, each litre of replacement solution should also contain about 16 mEq of potassium and 45 mEq of bicarbonate to replace these electrolytes

The amount of potassium required to replace the deficits in acute cholera should be sufficient to prevent complications without producing toxicity Ideally, measured potassium losses in urine and fæces would be exactly replaced, but facilities for this are rarely available in areas where cholera remains a problem, and even if they were the demands on time, personnel, and the laboratory during an epidemic would preclude their use except in the exceptional patient

It therefore seems advantageous to add a small amount of potassium to each bottle of replacement solution But the rapid infusion of 3–4 litres of a potassium-containing solution during the initial treatment of shock and collapse might increase the plasma-potassium levels too much, with the danger of heart-block and other conduction defects Until further information is available it is advisable to use parenteral potassium only after the initial dehydration has been treated, and when maintenance solutions are given more slowly

For the treatment of potassium depletion in infantile diarrhœa, Govan and Darrow (1946) recommended a solution containing 35 mEq of potassium per litre which he never gave at the rate of more than 120 ml per hou In adults, Nadler et al (1950) reported no untowar effects in treating the potassium depletion of diabet acidosis and prolonged vomiting with an isotonic solutio of potassium chloride (155 mEq per litre) given intravenously at a rate of 290 ml per hour (45 mEq potassiu per hour) But these infusion rates are far less than we have found necessary to maintain hydration in cholera patients, and an infusion-rate of 100 ml per minute is

, for the rapid treatment of collapse during the period of rehydration

Without electrocardiographic or laboratory control, which is impossible during the treatment of large numbers of acutely ill cholera patients, a solution is needed that is safe under a variety of conditions The addition of 10 mEq (7 5 g) of potassium chloride to 1 litre of saline should satisfy this need, and during an epidemic this solution could be used with safety in remote areas, even without medical supervision It will replace at least half the initial potassium deficit in the average severe case, and it should prevent the major complications of potassium deficiency As long as diarrhœa continues 10 mEq potassium may be added to each litre of maintenance solution with impunity, even when the renal function is unknown because potassium will continue to be lost in concentrations of 10–50 mEq per litre of fæces (Watten et al 1959) With cessation of diarrhœa, if renal function is not satisfactory, potassium should be discontinued In uncomplicated cases, 10 ml of a palatable mixture containing 100 g each of potassium citrate, potassium acetate, and potassium bicarbonate per litre of water may be diluted and given by mouth three times a day as soon as nausea and vomiting cease

From the electrolyte data reported in this paper, and from knowledge of experimental and clinical potassium depletion, one can conclude that the recommended addition of potassium should provide a more physiological approach to cholera therapy, diminish complications, and further reduce the mortality-rate

The opinions and assertions contained herein are those of the authors and they are not to be construed as official or as reflecting the views of the Navy Department or the Naval Service at large.

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“ One of the explanations why people in general are rather well satisfied by living and working in these regulated national communities of the Western World is undoubtedly that they do not notice the controls so much, or do not react so violently, as they are becoming accustomed to them The present level of taxation in all Western countries, for instance, would have been unthinkable fifty or even twenty years ago There is a deep truth in Albert Einstein's observation that if there were beings who were flat and without thickness and who lived on the surface of a sphere, they would have no idea of a third dimension Like domesticated animals, people growing up in the Western type of regulated national communities have no real conception any longer of a wilder life. To the reflecting social scientist the adaptability of the human animal to new conditions will never cease to be one of this world's wonders ”
—GUNNAR MYRDAL. *Beyond the Welfare State* London 1960

FALLACIES IN INTERPRETATION OF QUECKENSTEDT'S TEST

A R TAYLOR
M.A., M B Aberd, F R.C S.E
NEUROLOGICAL SURGEON, ROYAL VICTORIA HOSPITAL, BELFAST

IN 1916 Queckenstedt introduced his test for the detection of spinal subarachnoid obstruction He noted that compression of the jugular veins caused a “congestion of the brain”, and consequent increase in the cerebrospinal-fluid (C S F) pressure In the presence of an expanding spinal lesion sufficient to block the subarachnoid space, this increase is not transmitted to the spinal canal, and is therefore not reflected in the fluid level of a lumbar manometer Queckenstedt wrote of congestion of the brain Had this conception been retained, and not replaced, as it was, by that of increased intraventricular pressure, later confusion might have been avoided As the original test was modified, and combined cisternal and spinal puncture methods were introduced to define the site of obstruction more precisely, inaccuracies in the interpretation of results appeared

The first refinement was added by Ayer (1921) who, having perfected his technique of cisternal puncture, used it in combination with lumbar puncture to show a rise in cisternal pressure without a coincident lumbar increase as additional evidence of spinal obstruction.

About 1924, at least three workers—Fremont-Smith, Cushing, and Eskuchen—independently described a method of combining ventricular with lumbar puncture to confirm the diagnosis of posterior-fossa obstruction, but here conditions are dissimilar to those in the spinal theca, and the test thereby becomes less reliable

Further improvements in detail were added. Poppen and Hurxthal (1934) pointed out that before evidence of block is manometrically apparent, the subarachnoid obstruction must develop to a degree in which the area left for fluid circulation is less than the area of cross-section of the spinal-puncture needle. Stookey and Klenke (1928) placed the test on a firmer mathematical and mechanical basis by explaining the delayed rise and the rise maintained after removal of jugular compression. Grant and Cone (1934) applied graduated pressures to the neck by a manometer cuff in steps of 5 and 10 mm Hg and recorded them, with successive C.S F-pressure readings, on a chart. This obviated the individual variants of degree and site of finger compression, and gave comparable records compiled by different observers

Antoni (1931), at the Copenhagen clinic, modified the combined cisternal and spinal test. He postulated that, as the superior caval venous pressure decreased with the inspiratory expansion of the thoracic cage, and the inferior caval venous pressure increased with the descent of the diaphragm the cisternal level should fall and the lumbar pressure rise with each inspiration, if a block existed between the needles Wagner (1947), reporting over 800 double punctures from the same clinic, concluded that the test for “respiratory block” was not reliable because the communicating vertebral venous system equalised the pressure between the superior and inferior caval systems

In the “reversed Queckenstedt test” saline is injected into the sacral epidural space raising the pressure at that level The absence of a corresponding rise at a higher lumbar site signifies subarachnoid obstruction between the two needles

As a result of these combined methods, many observers, instead of thinking in terms of venous distension causing increased pressure, thought instead of columns of C.S.F moving from one part of the cerebrospinal axis to another For example, Elsberg (1941) said “The compression of the jugular veins causes a venous congestion within the cranial cavity, and as a result, the expulsion of C S.F from

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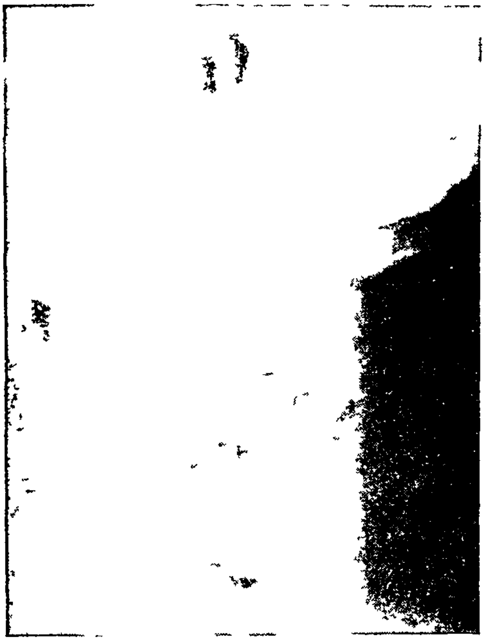

Fig 1—Injection into the internal jugular vein of a living subject with both jugular veins compressed

Contrast medium is seen filling the vertebral venous systems of the same side as far as the lower cervical region

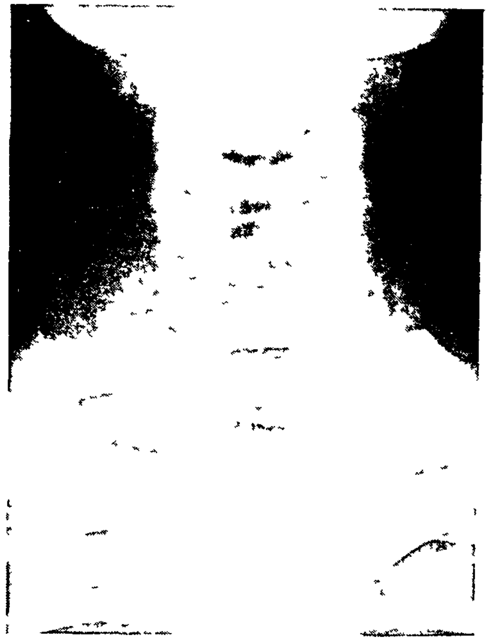

Fig 2—Injection into the jugular bulb in a cadaver with jugular veins compressed

The vertebral venous system is filled on both sides to the lower cervical level

the ventricular cavities" This misconception of rising ventricular pressure was encouraged by Dandy and Blackfan's (1914) theory that the rise in C S F pressure was caused by congestion of the choroid plexuses and increased fluid production in the ventricles Becht (1920) disproved this by showing that C S F pressure returned to its initial level within 11 seconds after release of jugular compression, but took 6 minutes to return after the volume of C S F was increased by the subarachnoid injection of saline

That venous and C S F pressures move in parallel was shown by Weed and Flexner (1921) in dogs, the fluid pressure increase bearing an almost constant relationship of 65% to the venous Bedford (1935) confirmed this In looking for the explanation of apparent anomalies in the results of Queckenstedt's test, attention must be focused on the changes attending intracranial venous distension as such, rather than those attending a rising C S F pressure in the ventricles, or elsewhere in the cranial cavity

Evidence for Posterior-fossa Obstruction by Queckenstedt's Test

After the introduction of ventricular puncture, some workers—e g , Gardner (1928) and Smyth and Henderson (1938)—sought to show that, on jugular compression, pressure rose higher in the ventricle than in the spinal canal if there was obstruction in the posterior fossa

O Connell (1943) drew attention to the fact that rise in pressure, measured through a wide-bore ventricular needle was much more rapid than through a narrow-gauge spinal needle, and that pressure rises in manometers connected to ventricular and spinal needles should not be directly compared

To eliminate this error, recordings were made of a series of combined ventricular and lumbar punctures, using a blunt fine-bore ventricular needle of the same gauge as the lumbar one Jugular, thoracic, and abdominal compression were successively performed, and manometer readings were recorded in the ventricle and spinal theca The series observed included some patients with normal intracranial pressure, and others with proven obstruction at the tentorium and aqueduct, or at the foramen magnum In none of these did the ventricular pressure rise higher or more rapidly than the lumbar pressure There was apparently some mechanism whereby pressure was equalised throughout the cerebrospinal axis even when the pathways were obstructed That this mechanism resides in the vertebral venous system is seen at surgical exposure of the posterior fossa

When jugular pressure is applied, there is a rapid outflow of C S F from the fourth ventricle, and the cerebellum is displaced downwards, but, in addition, there is distension of the whole venous bed in the posterior fossa and in the visible upper region of the cervical spinal canal Plainly, therefore, a rise in pressure caused by distending this venous bed will be transmitted to the C S F pathways whether there is obstruction at the tentorium and fourth ventricle or not Outflow of C S F from the fourth ventricle may be impeded, but displacement of venous blood into the cerebellar and spinal veins will not Obstruction in the posterior fossa may sometimes

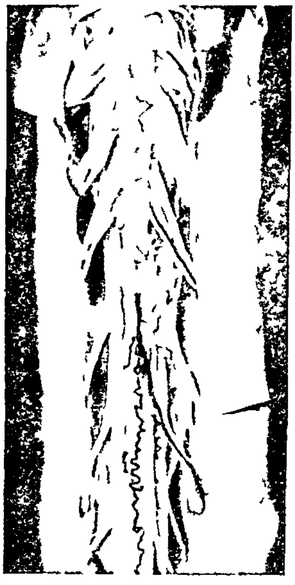

Fig 3—Spinal canal in the injected cadaver filled with dye to C7

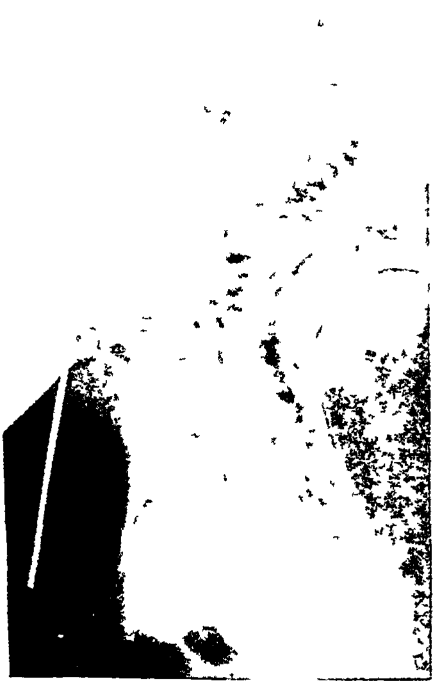

Fig 4.

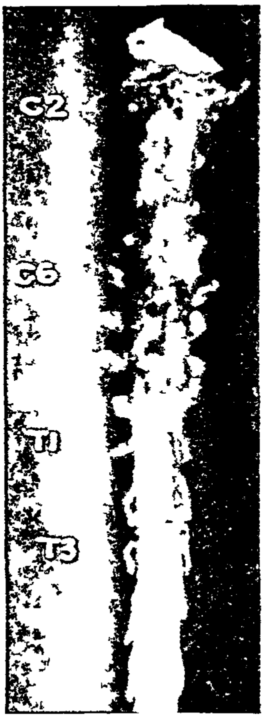

Fig 5

Fig 4—Injection into jugular vein of a rhesus monkey with all jugular veins tied off.

Dye fills the vertebral venous system and escapes to the innominate veins at the lower cervical level.

Fig 5—The monkey's spinal cord, showing the level of venous filling.

delay the rise of fluid in a spinal manometer on jugular compression, but it will not prevent it.

Obstruction in the Cervical Canal

A negative Queckenstedt test in the presence of obstruction in the cervical C.S.F. pathways is less easily understood, but has often been described.

Symonds and Meadows (1937) analysed seven cases of tumour at and below the foramen magnum. In none was a complete manometric block demonstrated, although in four the rise or fall was described as being a little delayed. In the one case in which a satisfactory myelogram was obtained, complete spinal block was demonstrated. These workers were led to conclude that "the degree of subarachnoid block, in relation to the severity of the clinical symptoms, would appear to be less in these cases of high cervical tumour than it is at a lower level." It is more likely that the degree of subarachnoid block is as great, but the methods of detecting it are subject to error.

Martin and Kleyntjens (1950) described three lumbar punctures performed on cases of meningioma at the foramen magnum. Two showed a slow rise and fall of pressure, and one had normal responses to jugular compression. They said "Queckenstedt's test shows little, a complete block being quite exceptional."

Weinstein and Wechsler (1940) described a dermoid tumour in the foramen magnum in which the Queckenstedt responses were normal. Congenital deformities in this region may also cause spinal obstruction. Gustafson and Oldberg (1940) described four lumbar punctures in their series, two partially blocked and two without evidence of block.

List (1941) recorded five cases of platybasia, four partially blocked and one quite free as judged by spinal manometry. In the last case the spinal cord was reduced by pressure to a fibrous-looking band of small calibre.

I have observed seven cases of neurinoma or meningioma between C1 and C4 in which subarachnoid obstruction appeared to be complete at myelography or operation, although Queckenstedt's test was negative.

Experimental Evidence

It seemed likely that, as in the posterior fossa, the obstruction was being bypassed by transmission of increased venous pressure through the vertebral plexuses. Evidence in favour of this hypothesis was collected from venous-injection studies in man and animals.

A catheter was inserted into the internal jugular vein of patients undergoing carotid angiography. With both jugular veins occluded on the cardiac side of the catheter, injections of contrast material were made. Fig 1 shows the intracranial venous distension spreading into the internal and external vertebral venous plexuses as low as C6–7. Injections of barium and dye into the jugular veins of cadavers cephalad to the point of venous obstruction confirmed this. X-rays showed a similar filling of the vertebral venous system (fig 2), and the spinal canal was shown to be filled with dye as far as C7 (fig 3).

Similar injections were made in monkeys after tying all the jugular veins. X-rays showed the filling of the vertebral veins and the escape back to the innominate veins and the heart (fig 4). The cord and dura preparation shows that the vertebral venous plexus filling extended, as in the human subjects, to the level of the lower cervical spinal canal (fig 5).

Provided, therefore, that a cervical spinal tumour does not obstruct the extradural as well as the intradural spinal veins, jugular compression will cause distension of the vertebral venous plexus as low as C6–7, with compression of the theca below the obstruction and a rise in pressure at the lumbar manometer. This rise may not be as great as that normally produced by this distension plus the C.S.F. displaced from within the skull to the spinal canal and thence to the manometer, but it may be sufficient to deceive even an experienced observer. (And in the event,

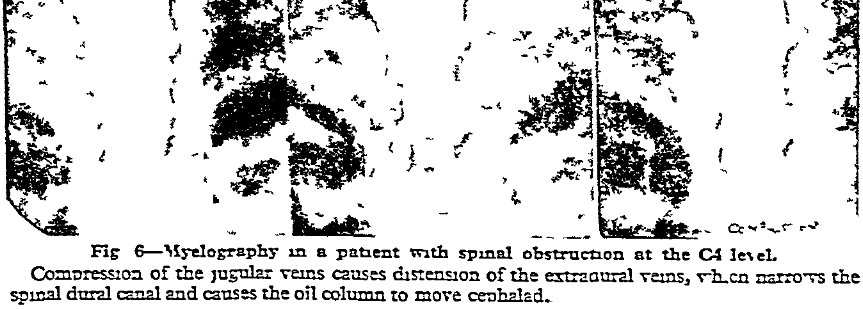

Fig 6—Myelography in a patient with spinal obstruction at the C4 level.

Compression of the jugular veins causes distension of the extradural veins, which narrows the spinal dural canal and causes the oil column to move cephalad.

most lumbar punctures are delegated to the inexperienced) This conception is very important for the understanding of C S F mechanics, because many theories about spinal pressures in Queckenstedt's test have been based on the elasticity or otherwise of the dura, which was presumed to be expanded by the increase of C S F, volume within If the theca is compressed from without in the presence of cervical spinal obstruction, it clearly does not matter whether the dura possesses elastic properties or not If pressure changes are transmitted past a spinal obstruction by extradural venous distension, myelography in such a case should show the oil column narrowing and moving cephalad on jugular compression Fig 6 shows that this does in fact occur

Discussion

The elaborations of Queckenstedt's test by combined puncture methods led to attention being concentrated on changing C S F pressures rather than changing venous pressures The realisation that C S F and venous pressures move in parallel did not help, because observers came to think in terms of increased ventricular pressure being transmitted via the aqueduct to the cisterna magna and the spinal canal in one continuous wave, with obstruction at any point halting the wave As a result, it has been suggested at different times that Queckenstedt's test could help in the diagnosis of aqueduct stenosis, acoustic neurinoma, foramen-magnum tumour, or obstruction of a ventriculocisternal (Torkildsen's) tube The above experiments have shown that it will do none of these things Nor is it a reliable test for cervical spinal obstruction above the level C5–6, unless the extradural as well as the intradural vertebral veins are completely obstructed by the agent compressing the spinal cord A negative Queckenstedt's test should not, therefore, be allowed to cloud clinical judgment in patients showing evidence of cervical spinal-cord compression above this level

Summary

The modifications of Queckenstedt's test are reviewed

Combined cisternal and spinal puncture methods tended to obscure the importance of venous distension as the primary cause of rising cerebrospinal-fluid pressures, as indicated by manometers

Clinical and experimental evidence shows that Queckenstedt's test is unreliable in detecting obstruction of the cerebrospinal-fluid pathways above the C6 level

Acknowledgment is made to Dr W H T Shepherd, of the Royal Victoria Hospital, Belfast, and to Dr Robert Saffley, of the Bangour Hospital, Edinburgh, for their help with the X-ray studies, to the department of microbiology of the Queen s University of Belfast, where the animal experiments were done, and to Mr R G Wood for the photographs

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ANTICONVULSANTS AS A FACTOR IN MEGALOBLASTIC ANÆMIA IN PREGNANCY

P B B GATENBY
M D Dubl, F R C P I, M R C P
VISITING PHYSICIAN, ROTUNDA HOSPITAL, DUBLIN,
PHYSICIAN, MEATH AND DR STEEVENS' HOSPITALS, DUBLIN,
PROFESSOR OF CLINICAL MEDICINE, TRINITY COLLEGE, DUBLIN

THERE have been many reports of megaloblastic anæmia induced by anticonvulsant drugs—an association first described by Badenoch in 1954 The relevant literature is well summarised by Hawkins and Meynell (1958) This anæmia has followed the administration of phenobarbitone and phenytoin, and also primidone In 1956, Girdwood and Lenman drew attention to the similarity in chemical structure between folic acid and these compounds They suggested that these drugs interfered with folic-acid metabolism This was confirmed to some extent by Chanarin et al (1958) who studied a patient in whom megaloblastic anæmia developed after primidone therapy They found that both the absorption and storage of folic acid in the tissues were normal and concluded that interference with tissue metabolism rather than deficiency of folic acid was the cause of the anæmia Recently a similar condition was described in a case treated with phenobarbitone (Chanarin et al 1960) Hawkins and Meynell (1958) investigated the incidence of macrocytic anæmia in large numbers of epileptics who were being maintained with these drugs, and found that this complication was rare Macrocytosis was common, however, in these patients, and 45% of those receiving phenobarbitone and phenytoin showed this feature This macrocytosis could be corrected with folic acid

Megabloblastic anæmia in pregnancy is now being recognised more often, and many reports have been analysed by Chanarin et al (1959) In the same paper, these workers produced evidence of a folic-acid deficiency in two-thirds of those nearing the end of their pregnancy, and in all patients with twin pregnancy All pregnant patients with megaloblastic anæmia were found to have a still greater deficiency of folic acid

Consideration of all these reports suggests that megaloblastic anæmia is more likely to develop when anticonvulsants are used in pregnancy Possible interference with folic-acid metabolism by these drugs is likely to increase the effect of the relative folic-acid deficiency which may occur in pregnancy Though Dimsdale (1959) drew attention to the danger of drug-induced megaloblastic anæmia in epileptics during pregnancy, no report of this complication has yet been found

In a recent survey of 100 cases of megaloblastic anæmia in pregnancy seen at the Rotunda Hospital (Gatenby and Lillie 1960), it was noted that 3 of the cases were epileptics receiving anticonvulsants The incidence of epilepsy in the general attendance at this hospital is approximately 1 in 400, so that the incidence of 3%

TABLE I—ANTICONVULSANTS AND MEGALOBLASTIC ANÆMIA IN PREGNANCY

Anticonvulsant drugs	Number of patients	Number of pregnancies	Incidence of megaloblastic anæmia
Phenobarbitone	28	48	0
Phenobarbitone and phenytoin	7	7	4*
Phenobarbitone and primidone	1	1	0
Methoin (Mesontoin)	1	1	0
No treatment	7	13	1
Total	44	70	5

* 1 unconfirmed

ngst the cases of megaloblastic anæmia suggested a ual relationship.

The records of all pregnancies in epileptics over a six- period (1953 to 1958 inclusive) were studied. 70 nces occurred in 44 epileptics. In 7 of them (13) no anticonvulsants were being adminis-, because there had been no attacks for many years. case of megaloblastic anæmia occurred in this group. The remaining cases were divided into groups depending on the anticonvulsants used. Table I shows the relative incidence of megaloblastic anæmia. There were no cases in 48 pregnancies treated with phenobarbitone alone. There were 4 cases (1 unconfirmed by bone-marrow biopsy) out of 7 treated with phenobarbitone combined with phenytoin.

In table II details are shown of the established cases. All had severe megaloblastic anæmia which responded briskly to folic acid by mouth, 20 mg. daily, in spite of continuation of the anticonvulsant treatment. Case C is noteworthy because phenobarbitone alone had been administered in previous pregnancies without the development of megaloblastic anæmia. None of these cases had achlorhydria. Cases A and B are still under observation and neither has shown radiological evidence of gastrointestinal abnormality.

TABLE II—MEGALOBLASTIC ANÆMIA IN PREGNANT EPILEPTICS RECEIVING PHENYTOIN

Case	Pregnancy	1st Hb estimation	Onset of anæmia	Hb at onset	Reticulocyte-peak with folic acid
A	2nd (no treatment during 1st)	11·1 g. per 100 ml. at 24th week	6 weeks antepartum	5·8 g. per 100 ml.	12% on 5th day
B	1st	8·1 g. per 100 ml. at 32nd week	4 weeks antepartum	4·3 g. per 100 ml.	14% on 6th day
C	6th (phenobarbitone during previous pregnancies)	12·4 g. per 100 ml. at 24th week	2 days antepartum	6·4 g. per 100 ml.	15% on 6th day

Summary and Conclusions

From this analysis, it appears that there is a high incidence (3 out of 7) of severe megaloblastic anæmia when phenytoin together with phenobarbitone is used in the treatment of epilepsy in pregnancy. It is recommended that, if phenytoin is being administered to an epileptic during pregnancy, either oral folic-acid supplements should be given during the last trimester, or frequent hæmoglobin estimations should be done to detect the onset of anæmia. If it proves to be megaloblastic, it will respond well to folic acid, the anticonvulsant treatment need not be interrupted.

The incidence of megaloblastic anæmia in 57 pregnancies in epileptics receiving anticonvulsant therapy was studied retrospectively. There were no cases in 48 pregnancies where phenobarbitone alone was used. In 7 pregnancies where phenytoin was used as well as phenobarbitone there were 4 cases (1 unconfirmed) of severe megaloblastic anæmia. Folic acid cured the anæmia in these cases, while allowing the anticonvulsant therapy to be continued.

I wish to thank Dr. E. W. L. Thompson, ex-Master of the Rotunda Hospital, for permission to publish this report of patients who were under his care. I am greatly indebted to Dr. H. C. Moore, pathologist, for his assistance.

References at foot of next column

HYPONATRÆMIA AND IMPAIRED RENAL TUBULAR FUNCTION WITH CARCINOMA OF BRONCHUS

J. RUSSELL REES *
M.A., M.D. Cantab., M.R.C.P.
MEDICAL REGISTRAR

S. B. ROSALKI
M.B. Lond., M.R.C.P.
REGISTRAR IN CHEMICAL PATHOLOGY

A. D. W. MACLEAN
M.B. Lond.
HOUSE-PHYSICIAN

THE GORDON HOSPITAL AND VINCENT SQUARE LABORATORIES OF WESTMINSTER HOSPITAL, LONDON, S.W.1

HYPONATRÆMIA is associated with reduced osmotic activity in the extracellular fluid and may occur with lowered, normal, or increased body-sodium stores. It may follow sodium depletion, water retention, or reduction in cellular osmolarity (Schroeder 1949, Sims et al. 1950, Rapoport et al. 1951, Danowski et al. 1955). Renal handling of sodium is variable, and retention or abnormal urinary loss may occur (Rapoport et al. 1951, Schwartz et al. 1957, Orloff et al. 1959).

Hyponatræmia may be found in adrenal failure and severe cardiac, renal, or hepatic disease. It has been described in tuberculosis, cerebral disease, and diabetes, and after excessive loss of body secretions by any route (Danowski et al. 1955, Elkinton 1956).

It may develop during acute lobar pneumonia and tuberculosis (Atchley et al. 1923, Winkler and Crankshaw 1938, Sims et al. 1950). A patient with bronchial carcinoma who showed hyponatræmia and abnormal renal chloride loss was described by Winkler and Crankshaw (1938). Recently, Schwartz et al. (1957) reported two patients with carcinoma of the bronchus in whom hyponatræmia and renal sodium loss probably resulted from inappropriate secretion of antidiuretic hormone. We describe here a further patient with a bronchial neoplasm and hyponatræmia in whom this mechanism did not operate. As well as deficient sodium retention, he had aminoaciduria and increased phosphate excretion. The presence of an acquired renal tubular defect is suggested.

Case-record

A stoker, aged 53, was admitted to the Gordon Hospital on April 17, 1959. For two months he had suffered malaise, non-productive cough, and loss of appetite, with particular revulsion for sweet and starchy food. He had lost 17 lb., and in the previous fortnight had suffered from nausea, with vomiting on four occasions. During the same period he had noted cramps in the abdomen and legs.

He had had a dry mouth and increased thirst for a week before admission. On April 15, he had fainted, and had since been confined to bed. There was no disturbance of micturition, but he had been constipated for a fortnight. He had been a moderate pipe smoker for years, and took little alcohol.

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* Present address: Guy's Hospital, London, S.E.1.

DR. GATENBY: REFERENCES

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TABLE I—DAILY INTAKE, OUTPUT, AND SERUM-ELECTROLYTE LEVELS

Day	Sodium intake (mEq)		Fluid intake (ml)		Urine (ml or mEq daily)				Serum (mEq per litre or mg per 100 ml)					
	Oral	I V	Oral	I V	Volume	Na	Cl	K	Na	Cl	K	Blood-urea	Total protein	—
1	0	0	1090	0	810	79	48	23	109	82	3 4	35	6 4	
2	0	0	2160	0	—	—	—	—	111	84	4 5	36		
3	0	0	1920	0	—	—	—	—	—	—	—	—		
4	0	0	1230	0	1380	108	68	57	—	—	—	—		Vomit 360 ml
5	68	0	1860	0	1360	24	16	45	107	78	—	32		Vomit 360 ml
6	102	185	2250	2280	4320	117	177	95	110	77	5 7	35		
7	102	105	2970	3090	2900	128	130	59	121	84	5 6	22		
8	102	185	2010	1980	3360	70	52	12	113	83	1 3	23		
9	102	335	1830	3540	3220	245	280	28	112	80	3 2	24		
10	102	335	1980	3030	1910	168	196	19	123	97	3 9	—		
11	68	300	1590	1650	—	—	—	—	121	95	3 6	21		
12	68	160	750	1140	1140	145	138	34	127	97	4 7	36		
13	68	160	120	1140	1000	122	—	57	126	95	1 3	38	5 4	
14	68	160	510	1140	970	123	159	75	131	94	4 5	—		
15	68	160	510	1140	1200	156	199	79	132	106	1 7	57		
16	68	160	510	1140	1000	74	90	100	—	—	—	—		
17	68	100	1110	750	815	64	86	88	—	—	—	—		
18	136	0	1350	0	700	55	90	82	133	100	3 2	70	5 1	
19	136	0	1980	0	—	—	—	—	136	101	5 0	79		
20	0	0	1500	0	790	53	73	79	142	95	4 3	62	5 1	
21	0	0	1210	0	1040	5	16	125	127	102	4 6	75		

— indicates no measurement, 0 indicates no intake On days 11 and 19, the collection was lost Day 1 is a 12 hour collection (6 P M –6 A M) Day 12 is an 18 hour collection I V = intravenous

Examination

He was thin and wasted There was no clinical dehydration or œdema No abnormal pigmentation was noted B P 100/60 mm Hg Respiratory system fine râles at bases of both lungs, otherwise normal The tongue was furred, but the mouth was not dry

Investigations

Daily serum-electrolyte and blood-urea levels, urine-volumes and electrolyte content, and fluid and sodium intakes are shown in table I and in figure

Blood —Hæmoglobin 15 0 g per 100 ml Erythrocyte-sedimentation rate (Wintrobe) 11 mm in the first hour Total white-cell count 9000 per c mm (neutrophils 70%, lymphocytes 30%) Liver-function tests, serum-amylase, and serum-cholesterol normal Serum-albumin 3 9 g per 100 ml Serum-globulin 2 5 g per 100 ml Random blood-sugar 123 mg per 100 ml Wassermann and Kahn tests negative Serum-alkali reserve (day 13) 24 mEq per litre Serum-alkaline phosphatase 7 King-Armstrong units Serum-calcium 10 6 mg per 100 ml , serum-inorganic phosphate 2 2 mg P per 100 ml (day 2) Serum-calcium 13 3 mg per 100 ml , serum-inorganic phosphate 1 6 mg P per 100 ml (day 14) Serum-creatinine 0 6 mg per 100 ml (day 14)

Urine —Urinary calcium 350 mg per 24 hours Urinary phosphate 480 mg P per 24 hours Urinary creatinine 450 mg per 24 hours (day 14) Urinary aldosterone excretion (Dr R V Brooks) 1 8 µg per day (day 16), 1 7 µg per day (day 17) (normal range 3–8 µg per day with a mean of 5 µg) Steroid excretion is shown in table II

The specific gravity was always within the range 1 010–1 026 No albuminuria Intermittent glycosuria and ketonuria There was no glycosuria after day 13, and no ketonuria after day 18 Paper chromatography of urine for aminoacids (Dr J H Wilkinson) showed (1) a large increase of alanine, glycine, glutamine, histidine, lysine, threonine, and γ-amino butyric acid, (2) a moderate increase of glutamic acid, taurine, and serine, (3) small quantities of valine, leucine, and tyrosine, and (4) traces of methyl histidine and cystine This pattern of generalised aminoaciduria was present up to the time of death

Sputum —No malignant cells

X-ray of chest —Mass in left lung near hilum, with bilateral hilar-gland enlargement Normal pulsation and diaphragmatic movement on fluoroscopy

Isotope studies (Dr J F Zilva, Dr J P Nicholson) —Total exchangeable sodium (day 12) 2540 mEq = 54 1 mEq per kg (normal range 37–56 mEq per kg) Total exchangeable potassium (day 12) 2530 mEq = 54 1 mEq per kg (normal range 37 5–64 mEq per kg) Na/K = 1 00 (normal range 0 69–0 95) Bromide-space (day 13) 15 9 litres = 340 ml per kg , (day 14) 16 3 litres = 359 ml per kg (normal range for his build 248–378 ml per kg)

Electrocardiography —Day 1, alternating atrial flutter and fibrillation Fast ventricular rate of about 150 beats per minute with both rhythms Day 5, sinus rhythm, rate 80 beats per minute Tracings otherwise normal

Progress

The history of recent cough and the X-ray findings suggested bronchial carcinoma Severe hyponatræmia (109 mEq per litre) was found on admission and was associated with abnormal renal sodium loss (79 mEq in second half of day 1)

He gradually became worse He was moderately thirsty but too ill to drink unless assisted During the first four days he took sweetened fruit drinks only, and he continued to refuse food throughout the rest of his illness

Adrenal failure caused by bilateral metastatic deposits seemed unlikely with a normal blood-urea, a low serum-potassium (3 4 mEq per litre, day 1), and no pigmentation His blood pressure (95–100/60 mm Hg) was low but this was due to tachycardia, and it rose on day 4 to 120/80, when the arrhythmia reverted to sinus rhythm, though the hyponatræmia persisted (107 mEq per litre) He was so ill that it seemed best to give extra salt and sodium-retaining hormones until more was known of his adrenal function On day 5, oral salt in cachets and intravenous saline were begun (table I and figure), and he was encouraged to drink more He cooperated readily and high intakes were achieved between days 6 and 11 He also took a total of 6 mg fludrocortisone between days 5 and 9 This potent salt-retainer was used to avoid confusion in estimations of urinary steroid excretion which were done at this time Fludrocortisone was stopped as soon as these results were known

With this therapy there was slight improvement, though he remained weak The serum-sodium rose only slowly, and continued to rise when fludrocortisone was discontinued on day 8 and sodium intake was increased Intensive sodium therapy was given up to day 11 by which time the serum-sodium level had risen only to 121 mEq per litre

Between days 12 and 16, water intake was reduced as much as possible to see if this would affect the renal sodium loss as in the cases of Schwartz et al (1957) Sodium supplements were continued, so that he also received 1140 ml fluid daily intravenously, and negative fluid balance was not, therefore, achieved In this period, with an intake of 228 mEq sodium daily, the serum-sodium level continued its slow rise to 132 mEq per litre From about day 12, his condition steadily worsened, with increasing back pain at the level of the lower part of the thoracic spine, and by day 17 he was very ill No more intravenous saline was given, but oral supplements were continued for another 2 days His fluid intake was about

1·5 litres daily. He became emaciated, and bronchopneumonia developed. Finally he lapsed into coma and became clinically dehydrated. There was a terminal rise in blood-urea levels, and the serum-sodium rose to a maximum of 142 mEq per litre on day 20, though it fell again the following day to 127 mEq. He died on day 22.

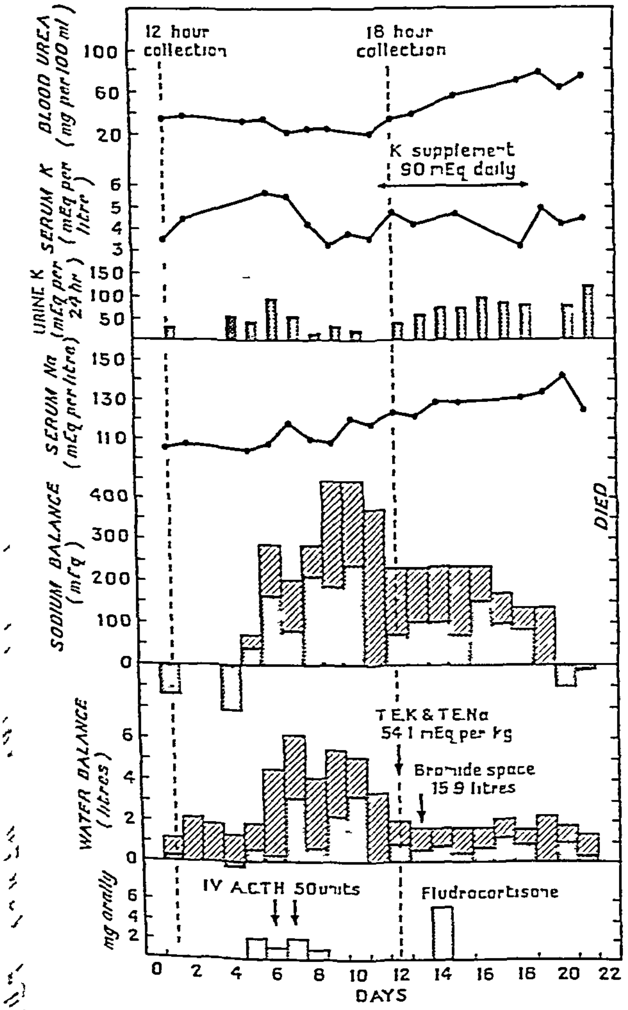
Necropsy

At necropsy (Dr J. S. Cornes) an oat-celled anaplastic carcinoma was discovered, originating in the lingular bronchus, and spreading to the lung, mediastinum, and left supraclavicular lymph-nodes. No other macroscopic spread was found, but histological examination showed infiltration of the liver and spleen by tumour cells.

The kidneys were macroscopically and histologically normal. Histochemical staining (Dr John Pryse-Davies) showed normal alkaline phosphatase, acid phosphatase, non-specific esterase, succinic dehydrogenase, and lactic dehydrogenase activity. Microdissection (Dr E. M. Darmady) revealed no abnormality.

The adrenals were enlarged (combined weight 22 g.) and histologically showed widening of the cortex principally in the zona fasciculata. Histochemical staining (Dr Pryse-Davies) for alkaline phosphatase, acid phosphatase, non-specific esterase, succinic dehydrogenase, and steroid 3-β-ol dehydrogenase suggested a hyperactive adrenal gland with increased steroid metabolism.

The parathyroids showed slight uniform enlargement. The pituitary contained a small developmental cyst, 3 mm. in diameter, but otherwise was normal.



Water and sodium balance calculated from intake and output figures with no allowance for extrarenal loss or water of metabolism.

Daily intake plotted up from baseline. Daily output plotted down from intake figures. Shaded areas above baseline represent positive balance, shaded areas below are negative balance. Intake data only for days, 2, 3, 11, and 19. For potassium, urinary figures only are shown. T.E.K. = total exchangeable potassium. T.E.Na = total exchangeable sodium.

TABLE II—URINARY STEROID EXCRETION

Day	Urinary steroids (mg per 24 hours)		Steroid therapy
	17-hydroxy-steroids	17-keto-steroids	
4	17·8	4·4	Nil
5	7·7	7·0	Fludrocortisone 2 mg. oral
6	66·0	16·8	Fludrocortisone 1 mg. oral Corticotrophin 50 units I.V.*
7	65·0	21·0	Fludrocortisone 2 mg. oral Corticotrophin 50 units I.V.
9	37·0	11·5	Nil
10	2·1	2·0	Nil
20	17·4	7·7	Nil
21	17·7	18·8	Nil

* I.V. = intravenous.

Discussion

The outstanding feature was the extreme hyponatræmia accompanied by malaise, cramps, and thirst. Mechanisms such as decreased cellular osmotic activity or a new steady state, which have been suggested to explain hyponatræmia in severe illness (Sims et al. 1950, Danowski et al. 1955) did not operate in our patient whose hyponatræmia improved as his clinical state deteriorated.

Addison's disease was not present, nor was there any evidence of the usual type of salt-wasting renal disease which is associated with obvious changes in the kidneys (Stanbury and Mahler 1959). The hyponatræmia was clearly associated, however, with deficient renal sodium retention. This is seen on day 1, and on day 4 when 108 mEq. sodium were excreted after at least 4 days without any salt intake. This sodium-leak was partially inhibited by fludrocortisone on day 5, but the presence of more than a trace of urinary sodium at this low serum-level (107 mEq. per litre) suggests that tubular response was impaired. By day 14, a large dose of fludrocortisone had no effect on sodium excretion showing that the tubular defect had increased.

Aldosterone excretion was reduced on days 16 and 17. By then massive sodium repletion had occurred. Extrapolating from the results on day 12 (allowing 10 mEq. daily for extrarenal loss), total exchangeable sodium is estimated at 2866 mEq. for day 16 (approximately 61 mEq. per kg.) and his serum-sodium had risen to a reasonable level for his clinical state. The low aldosterone excretion at this stage is therefore not surprising.

An estimate of the metabolic state on admission may be made from the isotope studies.

On day 13 the bromide-space was 15·9 litres (within normal limits), and before this marked positive water balance had occurred. Allowing 700 ml. daily as the balance between insensible loss and water of metabolism, a positive balance of 6·2 litres occurred between days 7 and 11. Unfortunately, the urine on day 11 was lost, but the intake makes a negative balance unlikely. Ignoring this day a positive balance of approximately 5·6 litres existed between days 5 and 13. Thus, on day 6, the extracellular fluid volume was estimated at 10·3 litres (about 220 ml. per kg.). This figure would have changed little from the time of his admission, and is abnormally low.

Total exchangeable sodium on day 12 was 2540 mEq. Ignoring day 11 again cumulative sodium retention from day 5 to day 12 was 972 mEq. The amount of food taken was negligible, and allowing 10 mEq per day for extrarenal sodium loss, the estimate for total exchangeable sodium on day 5 was, at most, 1640 mEq (approximately 35 mEq per kg)—an abnormally low figure Total exchangeable potassium on day 12 was 2540 mEq, and cumulative potassium loss in the previous week was 258 mEq (again ignoring day 11) Allowing 10 mEq daily for unmeasured potassium loss, the total exchangeable potassium on day 5 was estimated at about 2868 mEq (approximately 61 mEq per kg), which is in the upper normal range

Thus it appears that our patient on admission was depleted of sodium with a reduced extracellular-fluid space

In their two patients, Schwartz et al (1957) thought that carcinoma in some way caused inappropriate secretion of antidiuretic hormone This produced sodium loss by increased glomerular filtration and, because extracellular volume did not fall, by a failure of aldosterone secretion to rise with sodium depletion Both patients had severe hyponatræmia, in one case as low as 103 mEq per litre, with few symptoms In one the extracellular volume was measured, and was found to be raised

In our patient, the low estimate for extracellular space on admission makes it unlikely that inappropriate secretion of antidiuretic hormone caused his sodium loss The increased thirst in the week preceding admission is in keeping with this view, though thirst can occur with an increase in body water (Wynn and Rob 1954)

The effect of water restriction (days 12–16) was unimpressive There was no dramatic reduction in urinary sodium loss as in the patients of Schwartz et al (1957) and though restriction of water was not severe, it was more than was needed in one of their cases to reverse sodium loss Administration of large amounts of fluid caused improvement, rather than deterioration, and sodium given in this phase was largely retained in contrast to the results in their patients The poor response to salt-retaining hormones is a further point of distinction, and in addition our patient probably produced hypotonic urine on some days (e g, day 8, table I) when specific gravity was not recorded, whereas in the cases of Schwartz et al (1957) urine was hypertonic to plasma

In our patient, it seems that the renal sodium leak was due to impaired tubular function With liberal intakes, sodium loss was not excessive, and repletion was easily achieved However, when sodium intake was low, an obligatory renal salt-loss was revealed, leading to sodium depletion and, eventually, hyponatræmia

This defective reabsorption of sodium, together with intermittent ketonuria and glycosuria, suggested proximal tubular damage, and investigation led to the unusual finding of generalised aminoaciduria Other recognised causes of renal aminoaciduria were absent, and there was no evidence of the adult Fanconi syndrome (Wallis and Engle 1957) in which sodium loss, in particular, does not occur Overflow aminoaciduria may be found with increased protein breakdown, and since the plasma-aminoacid level was not estimated, this is a possibility in our patient, though other features favour its renal origin

Impaired phosphate reabsorption and low serum-phosphate levels accompanied the aminoaciduria, providing further evidence of proximal tubular damage The terminal hypercalcæmia and necropsy findings of parathyroid gland enlargement were probably due to secondary hyperparathyroidism

The distal tubular exchange mechanism of potassium for sodium could function normally as shown by falling sodium excretion in the last week, with increased potassium excretion and K/Na ratios, particularly evident on day 21 24-hour creatinine-clearance on day 14 was reduced, and rising blood-urea levels were recorded in the last week, indicating progressive reduction in glomerular filtration This might have reduced the load on the proximal tubules to a level at which they could function competently The resultant fall in distal tubular flow might then allow the efficient cation exchange and sodium conservation seen on day 21 A diminution in proximal tubular load would also explain the disappearance of glycosuria and ketonuria in the week before death

A defect in proximal tubular function was therefore thought to be present, and a similar defect was postulated by Rapoport et al (1957) as the cause of hyponatræmia in their patients with tuberculous meningitis However it remains difficult to explain the urinary composition on days 1 and 4 The metabolic state on admission should have resulted in maximal aldosterone secretion The modest potassium excretion and low urinary K/Na ratio at this time is surprising and, with the poor response to administered steroids, suggests that distal tubular function was also impaired

Summary

Severe hyponatræmia developed in a man of 53 with bronchial carcinoma He showed poor renal sodium conservation which, with negligible intake because of anorexia, had caused sodium depletion

Repletion was easily achieved and fluid restriction did not affect the sodium loss Metabolic studies suggested that, on admission, he was depleted of sodium, with a reduced extracellular-fluid volume

There was no evidence of adrenal failure, and at necropsy the adrenal glands were enlarged and showed signs of hyperactivity

The renal response to fludrocortisone and corticotrophin was poor There was no clinical evidence of any of the usual types of salt-wasting renal disease, and at necropsy the kidneys were normal on detailed histological examination

There was evidence of functional damage to the proximal tubules with generalised aminoaciduria, glycosuria, ketonuria, and increased phosphate excretion Aminoaciduria was constant throughout, but glycosuria and ketonuria were intermittent and disappeared in the last week

The distal tubular exchange of sodium for potassium was active terminally, though perhaps not on admission It is suggested that the sodium loss was mainly due to proximal tubular damage, and that the bronchial carcinoma had caused this unusual derangement of tubular function

We wish to thank Dr R D Tonkin, under whose care this patient was admitted, for permission to report this case, and Dr R I S Bayliss for advice on the manuscript The microdissection of th kidneys was carried out by Dr E M Darmady The urinary amino-acid determinations were performed by Dr J H Wilkinson We are indebted to Dr R V Brooks for the urinary aldosterone assays Details of the adrenal and renal histochemical studies were kindly provided by Dr John Pryse-Davies The results of the isotope studies were provided by Dr J F Zilva and Dr J P Nicholson The necropsy was performed by Dr J S Cornes The figure was prepared by the department of medical illustration, Guy's Hospital

References at foot of next column

POSTPARTUM PRE-ECLAMPSIA

I R McFADYEN
M B Glasg
FLIGHT LIEUTENANT, R A F
From the Royal Air Force Hospital, Aden

A WOMAN, aged 19, had an eclamptic fit fifteen hours after she had her first baby She had given no evidence of pre-eclamptic toxæmia while pregnant, or during her eight-hour labour An episiotomy was necessary for delivery, and, in the course of its repair, she seemed drowsier than would have been expected from the 100 mg pethidine and the gas-and-air analgesia she had received during labour That night she slept uneasily, complaining of epigastric discomfort, and at 6 A M next day her blood-pressure (B P) was 140/90 mm Hg an hour later she had the fit

The patient was first seen during the sixteenth week of pregnancy No history of serious illness, previous pregnancy, or fits was given (this was confirmed in the puerperium) Her general condition was excellent Hæmoglobin 87% (Haldane), blood-group B, rhesus-positive, Kahn-negative The B P was 130/70, weight 105 lb , and her urine showed no abnormality Thirteen visits were made during the pregnancy Apart from a trace of albumin in a morning specimen of urine at the thirty-seventh week, and slight swelling of the ankles the week before that, the only abnormality of the pregnancy was a degree of hydramnios at the thirtieth week sufficient to warrant an X-ray of the abdomen The hydramnios decreased slowly but was still present at term The weight rose gradually to 128 lb at term, and fell 1 lb in the following week The blood-pressure remained between 110/60 and 120/80 during the pregnancy

Progress

Day 1 —A healthy 6½ lb infant, born ten days after the estimated delivery date The labour was uneventful Total blood loss 8 oz , 0 5 mg of ergometrine was given intramuscularly after delivery of the placenta

Day 2 —B P after the fit, 140/90 There was no residual paralysis, but facial œdema was noted and this increased during the next few hours The patient was sedated with barbiturates, and given a low-salt diet During the day her B P remained at about 130/90 Morphine was given that night as she complained of headache

Day 3 —The B P fell until it was 125/80 in the evening, the œdema subsided, and the patient had no complaints

Day 4 —About seventy-two hours after delivery the frontal headache and facial œdema returned The breasts became engorged and treatment for the suppression of lactation was begun Her temperature rose until it was 102 6°F by the evening She was moved into an air-conditioned room, and sedated with 6 g amylobarbitone six-hourly and 25 mg chlorpromazine orally twice daily The hæmoglobin was 88% (Haldane) and the hæmotocrit value 40%

Day 5 —A morning catheter specimen of urine contained 200 mg albumin per 100 ml , 15–25 red blood corpuscles, and 3–4 white corpuscles per high power-field, it was sterile A Foley catheter was introduced and nitrofurantoin 100 mg given six-hourly to prevent a urinary infection She passed 1290 ml of urine that day The œdema and headaches remained The temperature fell to 98 4° by the evening The blood-pressure, however, started to rise during the day

Day 6 —The B P continued to rise until in the evening it reached 170/100 At that point 12 5 mg hydrallazine was given orally this was followed an hour later by a fall in B P to 145/100 The dose was increased by stages to 37 5 mg four-hourly The B P fell gradually, until on the tenth day it was consistently 130/80 at the time that the next dose was due

The typical pre-eclamptic facies and headache remained until the sixth day when, along with the albuminuria, they started to subside On the ninth day the catheter was withdrawn, the administration of chlorpromazine was stopped, and the patient was moved out of the air-conditioned room The output of urine did not fall below 950 ml per twenty-four hours, nor did the blood-urea rise above 20 mg per 100 ml and the blood-electrolytes remained within normal limits

The hydrallazine was continued until the fifteenth puerperal day It was gradually reduced thereafter, and was stopped on the twentieth day The B P had then been 105/75 for three days, there was an occasional trace of albuminuria, and the patient had no symptoms The baby was bottle-fed and thriving

Six weeks after delivery the patient was seen at the postnatal clinic She had suffered no headaches or swelling of the ankles since leaving the hospital, nor were there any other complaints The urine contained no albumin, the B P was 110/75, and she weighed 106 lb Uterine involution was satisfactory

Discussion

Stander et al (1946) described 21 cases of eclampsia occurring within thirty hours of delivery 13 of these had shown no evidence of antepartum pre-eclamptic toxæmia In 9 cases of postpartum convulsions in the first twenty-four hours of the puerperium published by Hofmeister and Brown (1953), 2 had given no previous signs of pre-eclampsia Theobald (1955) quotes 4 cases of antenatal eclampsia in patients known to have been normal at some time in the twenty-four hours before the fits It is clear that this fulminating eclampsia can also occur in the puerperium It is not, however, common for a patient to develop the pre-eclamptic syndrome for the first time after delivery and after a fit, in none of these series is it mentioned Hamilton (1953) states that hypertension and convulsions may be produced by intravenous ergometrine given at the time of delivery, but this is not accompanied by œdema and albuminuria, and the blood-pressure usually settles within four hours

There is a school of thought which holds that pre-eclamptic toxæmia and eclampsia are due to increased myometrial tension, pointing out that twins and hydatidiform moles are examples of an overdistended uterus being frequently associated with pre-eclampsia Theobald (1955) gives as one of his essential criteria for any hypothesis purporting to explain the genesis of eclampsia that it must afford a reasonable explanation of eclampsia occurring up to four days after delivery of the placenta, and many find this a stumbling-block in accepting this hypothesis

A possible explanation of my case can be obtained from the concept of pregnancy as "a kind of physiological Cushing's syndrome" propounded by J S L Browne and elaborated by F J Browne (1958) In this it is held that the adrenal cortex undergoes hyperplasia in pregnancy under the influence of the large quantities of corticotrophin produced by the hypertrophied anterior pituitary and the placenta, and Poideven's (1959) demonstration of the relationship of striæ gravidarum to adrenal cortical hyperfunction supports it The excess of corticosteroids produced has been demonstrated by Gemzell (1953) who

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found that in the last three months of normal pregnancy the blood level of 17-hydroxycorticosteroids is four times the normal non-pregnant value. This would produce œdema and hypertension were it not that the healthy placenta inactivates the excess of pressor substance. If, however, placental function is diminished below some critical value by placental ischæmia (as may occur in essential hypertension, in a primigravid uterus which has hypoplastic vessels, or in twin pregnancy) pre-eclampsia develops. The same investigator has also shown that immediately after delivery the corticosteroid level is seven times the normal, but that it falls to the non-pregnant level by the sixth puerperal day. It might be expected that this would produce hypertension as the placenta is no longer present. This, in fact, happens. Browne (1958) quotes findings, in Sydney and London, that 20–30% of women whose blood-pressure remains within normal limits throughout pregnancy and labour are hypertensive in the first three days after delivery.

I have recently seen two patients in whom the pre-eclamptic syndrome developed after normal pregnancies; a third patient developed hypertension after a forceps delivery, during which she received two doses of 0·5 mg. ergometrine each.

Case 1.—A patient, whose first pregnancy and puerperium were quite uneventful, delivered her second child after a three-and-a-half-hour labour at term, and was given 0·5 mg. ergometrine intramuscularly. Antenatally her B.P. had not risen above 125/75, nor was there any other abnormality. One and a half hours after delivery she vomited and complained of headache. Her B.P. was then 180/110. She was sedated with morphine. Six hours later the headache was still present and she had developed generalised œdema with typical pre-eclamptic facies. The B.P. was 155/100, and a swab specimen of urine contained albumin ++. Sedation was continued and the œdema gradually settled. Thirty-six hours after delivery the headache and œdema had disappeared, the B.P. was 125/85, but there was still albuminuria. Thereafter the puerperium continued normally. The patient was discharged on the tenth puerperal day, her B.P. being 130/80, and the urine contained a trace of albumin.

Case 2.—Normal labour after a second uneventful pregnancy. A single intramuscular dose of ergometrine was given after delivery. On the third day of the puerperium the patient developed headache, hypertension (155/100), and gross generalised œdema. These increased in severity on the fourth day and then responded to rest in bed, sedation, and chlorothiazide therapy. She left hospital on the twelfth day, but the œdema recurred when she was at home and did not disappear for some weeks. The patient was a midwife, and remembered a similar sequence of events after her first confinement.

Case 3.—A primigravida with an uneventful antenatal course, the highest B.P. reading being 130/65. After a twenty-five-hour labour she was delivered with forceps under pudendal block anæsthesia, because of second-stage delay. Ergometrine 0·5 mg. was given with delivery of the anterior shoulder. As the uterus tended to relax an intramuscular dose of 0·5 mg. ergometrine was given. One hour and fifty minutes after delivery she complained of nausea; the B.P. was then 170/105. The patient was sedated with amylobarbitone. The B.P. fell steadily: four hours after delivery it was 135/80, and it did not rise again. There was no œdema.

The development of the pre-eclamptic syndrome after emptying of the uterus in the first two of these cases could easily be interpreted in terms of the foregoing hypothesis. A similar transient hypertension to that occurring in the third case was noted after a cæsarean section where the patient also had a double dose of ergometrine, and it is probable that the rise in blood-pressure was caused by the ergometrine in both cases.

Summary

A case of postpartum pre-eclampsia with one eclamptic fit is described in a patient who had hydramnios but no pre-eclamptic toxæmia before delivery.

A possible explanation is that the already high blood-levels of 17-hydroxycorticosteroids during the last three months of pregnancy rise still more immediately after delivery, and do not fall to normal until the sixth puerperal day. Pre-eclampsia will occur in this period if, through ischæmia, placental function is reduced below some critical value. Postpartum pre-eclampsia may arise once the placenta is delivered, because the excess of pressor substance is then no longer inactivated, and hypertension and œdema result.

I wish to thank Dr. J. B. Hewitt for his encouragement in the preparation of this paper, and the Director General of Medical Services, Royal Air Force, for permission to publish.

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Preliminary Communication

HYALINE MEMBRANE FOLLOWING TOTAL BODY RADIATION

RELATION TO LUNG PLASMINOGEN ACTIVATOR

In 1940 Warren and Spencer[1] pointed out that hyaline membrane formation was the most definite of all changes produced in the lung by X-irradiation of the chest. These changes were observed after "chest wall doses" of 800–15,000 r. Though hyaline membrane was by no means pathognomonic of irradiation lung damage, its association with œdema, fibrosis, diminished inflammatory response, and hyalinisation of arterial walls was sufficiently unusual to enable irradiated lung to be distinguished from the non-irradiated. The pathogenesis of this lesion is not understood.[2]

Recently patients with far-advanced malignancies have been subjected to total body radiation (T.B.R.) at the National Naval Medical Center, utilising a $4\pi\ ^{60}$Co irradiator.[3] Clinical results are to be described elsewhere, but we wish to report that at necropsy hyaline membrane and fibrinoid deposits have been prominent in cases surviving at least two weeks after treatment.

Lieberman[4] has recently associated hyaline-membrane disease of children with deficiency of plasminogen activator in the lung. This tissue enzyme converts plasminogen to plasmin, the active fibrinolytic enzyme of the body. Lung normally contains high levels of plasminogen activator.[4,5] Lieberman reasons that because of the relative insolubility of lung plasminogen activator its action is primarily local. In situations where there may be a pathological deposition of fibrin in the lung, it would

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LUNG ACTIVATOR ASSAY

Dose T.B.R.	Number of dogs	Days after radiation	Result
1000r	1 1 1	[illegible] 6 7	Positive Negative* Negative*
800r	1 1 1 1 1 1	[illegible] 8 9 10 11 12	Positive Negative Negative Negative* Negative Negative
700r	1	9	Positive
600r	1	9	Positive
Controls	10		Positive

* Assayed for inhibitor—all positive.

be the activator's function to activate the fibrinolytic system and effect the fibrin's removal. Persistence of fibrin deposits due to a defect in this system would lead to hyaline-membrane formation[4] and fibrosis.

The fibrin-plate technique of Astrup as outlined by Lieberman[4] was utilised and in addition fortified with 0·01 M Ca ions. The latter are added to saturate the citrate of commercial bovine fibrinogen and obviate non-enzymatic lysis of the fibrin.[5] This technique is considered quite sensitive and specific for the detection of plasminogen activator.[7]

OBSERVATIONS

Lieberman[4] has well documented the presence of activator in normal adult lung and this has been confirmed by us in a case of traumatic death. Two men who had undergone T.B.R. therapy were investigated. One had received 450r T.B.R. for disseminated lung cancer 18 days before death, and the other 1500r T.B.R. 15 days before death. The latter had no associated malignancy and had been treated in conjunction with an attempted transplant of kidney. In both instances hyaline membrane was present in the lung. Intensity of membrane formation has generally been associated with high dosage and survival for more than 6–8 weeks after therapy.[6] In both cases the assay of lung tissue failed to demonstrate any plasminogen activator.

To follow the sequence of events eleven dogs were subjected to T.B.R. in similar fashion to the human subjects. The table shows the results of assays of lung activator at various intervals in these eleven dogs and in ten controls.

The absence of activator in the irradiated animals could be due to inhibition. Portions of lungs from three animals with absence of activator were homogenised and the homogenate was mixed with equal volumes of an active lung homogenate. In each case the activity of the normal lung was completely inhibited. The animals tested are indicated in the table by an asterisk.

None of the lung sections showed the classical signs of radiation lung damage, and often they were described as normal. Since several weeks are generally required for the development of hyaline membrane,[6] and the animals in this dose range of T.B.R. seldom survive beyond the second week, this finding might be expected.

COMMENT

In two men treated by total body radiation hyaline membrane was found in the lung. Plasminogen activator was apparently absent.

The enzyme soon disappeared from the lungs of dogs given T.B.R. of 800–1000r, but these showed no morphologic change suggestive of the first stage of either hyaline membrane or fibrosis.

Our findings are consistent with the production in irradiated lung of a potent inhibitor of plasminogen activation.

Further studies are in progress to assess the influence of drugs and radiation technique on the activator system in the lung.

The opinions expressed in this paper are those of the authors and not necessarily those of the Navy Department.

WILLIAM H. FLEMING
M.D. Georgia
Lieutenant, Medical Corps, U.S.N.R.
Head Special Studies, U.S. Naval Hospital

JENO E. SZAKACS
M.D. Rome
Lieut.-Commander, U.S.N.
Pathologist, U.S. Naval Medical School

THOMAS C. HARTNEY
M.D. Seattle
Lieutenant, Medical Corps, U.S.N.
Pathologist, U.S. Naval Medical School

National Naval Medical Center,
Bethesda, Maryland,
U.S.A.

E. RICHARD KING
M.D. Ohio
Captain, Medical Corps, U.S.N.
Chief of Radiology, U.S. Naval Hospital

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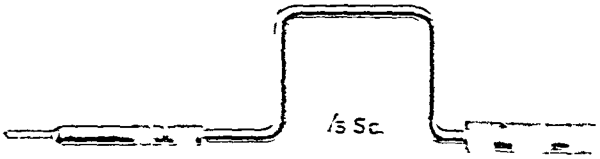
New Inventions

A BRACE SCREWDRIVER

ALTHOUGH Fitzgerald described a brace screwdriver several years ago[1] this has never become popular, and the ease with which screws can be inserted by its use has not been generally appreciated.

Repeated gripping of a conventional screwdriver and pronating and supinating the forearm, can be very tiring—as many as 150 repetitions of this movement being necessary to insert four screws. The brace screwdriver, by its continuous action, removes this strain and also eliminates the inertia of the screw which develops each time it stops turning. The lessened resistance diminishes the chance of the screw breaking and the brace gives better control.



The type of brace is important. The model here illustrated, adapted from a socket spanner, can be held firmly along the axis of the screw. There should be no sleeve on the crank handle so that the hand can appreciate small changes in resistance during insertion. Some screw-holding attachment is essential. A simple holding sleeve, made by the London Splint Co. for one of their conventional screwdrivers, was used at first and proved quite satisfactory. The Williams screw-holding device, made by Chas. F. Thackray Ltd., although more elaborate, could also be used for this purpose. The brace here illustrated uses the Stryker screw-holding attachment. The Stryker attachment was devised for a power-driven continuously rotating screwdriver, and it is particularly suited to the rotary action of the brace. It has the great advantage over any other screw-holding attachments that the chuck not only releases the screw head automatically but also allows the screw to be fully driven home and tightened by one continuous action, thereby avoiding the need to complete the last few turns with a conventional screwdriver.

This final pattern of brace screwdriver is available from Messrs. Down Bros. Ltd., 21 St. Thomas Street, London S.E.1. By its use screws can be inserted into the upper femur with appreciably greater speed and precision than by any previously available hand-driven device.

Liverpool Royal Infirmary,
Liverpool 3

GEOFFREY OSBORNE
M.CH. ORTH. Lpool, F.R.C.S.E.

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Reviews of Books

The Problem of Acute Hypothermia

Editor P M STARKOV Translated from the Russian by R E HAMMOND Editor of English edition E NEIL, M D, professor of physiology, Middlesex Hospital Medical School London Pergamon Press 1960 Pp 329 70s

THIS book contains the results of many years research in Professor Starkov's department in Omsk There are twenty-eight articles by the fourteen workers concerned, and they are all physiological, though the hope is expressed that some of the conclusions may be put to practical use The subject titles alone make interesting reading, for, as might be expected, they imply a quite different approach to the physiology of hypothermia from that in the Western world, where much of the work has been planned pragmatically, according to the needs and problems of the operating-theatre, and not so much concern, perhaps, is felt about the basic differences between the body functions at normal temperature and those revealed during hypothermia Physiologists will therefore welcome the results of study on such fundamentals as cold effects on blood-flow in limbs and viscera, on the effects of direct cerebral cooling, and the use in hypothermia investigation of the values accorded by such familiar parameters as those of the heart-lung preparation, decerebrate cat, isolated rat uterus, and skeletal muscle Behaviour and conditioned reflexes in puppies and adult dogs are subjects of natural interest to Russian physiologists, and the response of these nervous patterns to hypothermia is the subject of one of Professor Starkov's own articles

The publishers regret that for speed and economy of production the text is in typescript photolithography, but the quality of the pages is even and good, and the content more than makes up for any deficiency The translation is commendably clear

Lectures on Hæmatology

Editor F J G HAYHOE, M D, M R C P, department of medicine, University of Cambridge London Cambridge University Press 1960 Pp 247 60s

THESE lectures were delivered at Cambridge in December, 1959, at a course for physicians and clinical pathologists "having hæmatology as one of their main interests" Four of these lectures will interest any hæmatologist J V Dacie gives some facts from his unique experience in hæmolytic anæmia, W M Davidson provides an excellent account of iron metabolism and treatment, G Wetherley-Mein describes interestingly and practically what is meant by "myeloproliferative syndromes", and R M Hardisty makes a gallant attempt to bring together in a moderately coherent account what we now know about hæmostatic processes The other lectures are good, sometimes very good, reporting work that will be familiar to many hæmatologists R H Girdwood on megaloblastic anæmias, George Discombe on transfusion hazards, and J C White on hæmoglobin variants summarise their already published work Dr Hayhoe himself draws on some pages from his recent book on leukæmia Richard Doll writes on the incidence of leukæmia and the significance of environmental factors, D A G Galton on the chemotherapy of leukæmia, G I C Ingram on congenital and acquired disorders of blood coagulation, and J F Ackroyd on the pathogenesis of purpura H E M Kay brings together a useful summary of published results on attempts to use marrow transplants in the treatment of leukæmia

This sort of book falls between two stools the specialist in hæmatology will be interested only in the first four lectures we mentioned, the more general physician or pathologist with a main interest in hæmatology will hardly wish to buy a set of lectures that will need revision in a short time, especially when he can buy a whole textbook of hæmatology, containing nearly everything in this volume and a lot more, for rather less This volume is to be one of a series why not publish the others in a less expensive form—say, paper back with plastic binding and without some of the illustrations, none of which, in this hæmatology volume, are really necessary ?

Chemical Micromethods in Clinical Medicine

R H WILKINSON, M D, assistant chemical pathologist, The Hospital for Sick Children, London Oxford Blackwell Scientific Publications 1960 Pp 121 40s

EMPHASIS on micromethods in chemical pathology has increased steadily during the past twenty years It was gradually realised that blood-sugar and blood-urea were not the only substances that could be measured using capillary blood and that it was obviously more considerate and convenient to take small samples of capillary blood by needle-prick than larger ones from a vein by syringe It has also become clear that small amounts of heparinised blood may yield as much plasma as larger amounts of clotted blood can yield serum These considerations apply particularly to pædiatrics, and in this country notable contributions to microchemical methods have come from The Hospital for Sick Children, Great Ormond Street, and some very important ones from the author of this little book There are only about 100 pages of text, of which 10 are taken up by illustrations, not all of them essential (a page is used for a photograph of a Van Slyke manometer and another for its micro version, and almost a whole page is given to a photograph of the EEL flame photometer, which has been in routine use in virtually all pathology laboratories for many years) Most of the methods for examining blood in a pædiatric hospital are clearly described (the estimation of serum-iron is not among them) Micromethods only are considered, and this excludes many important pædiatric investigations of urine and fæces

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THE LANCET

LONDON 5 NOVEMBER 1960

Coming Home and Going Abroad

On achieving independence, a Colony naturally wants to have all its services manned by its own people, and that is something to which every new nation should look forward But commonly the wellbeing and progress of Colonies have depended largely on the devoted work of administrative and professional officers from overseas, and usually these ought to go on with that work until there are enough properly qualified indigenous officers to replace them Unfortunately the insecurity of a new regime may lead to an exodus of many of the men and women whom the new country will most need in the next few years The anxieties of a Civil Servant in a country likely to become self-governing are well depicted in the white-paper [1] issued last week

> " the sense of vocation which led him into the Public Service in an overseas territory still remains, but he is beset by uncertainty as to the extent to which he will be able to fulfil it under the new conditions his status in public affairs is changing and very often he and perhaps his family also are subject to discomforts stemming naturally from a period of rapid political change, and until reassurance is given him on the shape of his future he must live through a period of extreme doubt about the years ahead "

To prevent the " tragic waste of human skills and wisdom " inevitable where a service runs down through departure of its key members, the British Government, as announced last July,[2] are offering ten-year agreements to most Colonial territories by which the territory need pay little more to employ someone from overseas than to employ one of its own nationals [3] In respect of some 21,000 officers of the Overseas Civil Service (appointed by the Colonial Office or the Crown Agents) the Government will be responsible (1) for the expatriation or inducement element often added to basic salaries to attract overseas candidates, (2) for the corresponding part of the pension, (3) for education and children's allowances, (4) for half the cost of leave passages, and (5) for half the cost of compensation payable for premature retirement While this excellent scheme can be looked on as an act of justice towards people who have been encouraged to take overseas appointments under the Crown, it is also much more It is an important offer of assistance, during the transition period, to territories which may see the advantages of retaining expatriate officers but might otherwise be unable to keep them The cost to Britain is estimated at between £12 million and £16 million a year

Two years ago at the British Medical Association's conference on overseas appointments,[4] one speaker said bluntly that if men are expected to go and work in the Colonial Service, arrangements must be made for them when they come back An attractive suggestion which is firmly turned down in an appendix to the white-paper is that the Civil Services at home and abroad should be unified, so that members could expect a full career, if not in the Colonies then at home But in point of fact the home Civil Service, with an administrative staff of less than 2500, can offer comparatively few openings to men returning from abroad, and the vacancies now likely to be offered to such men by other Colonies will usually be in a basic grade, and for only one or two tours of service The creation of a unified service based on the United Kingdom would, it is felt, give a false impression, because it could create no jobs for which members of the Overseas Civil Service are not already eligible Though some of these will enter the home Civil Service, or the Foreign Service, or may be assigned to other countries under technical-assistance agreements or similar arrangements, they cannot be sure of such employment, and for this reason the Colonial Office in July, 1957, set up an Overseas Services Resettlement Bureau to find them, if need be, alternative posts Of 1710 applicants the bureau has so far found employment for over 1000—about 500 of them in the past year The Government hope that " the knowledge that the Bureau will be there to assist them when required will both encourage officers to continue their overseas service, and new recruits to join it "

To the returning doctor even less than to the administrator can the Government guarantee a post at home, and latterly the difficulty of getting one has been a misfortune both to those who applied and to the public which has often been denied their services The Government's own medical establishment is small and specialised, and the Ministry of Health, even when it accepts a moral obligation to get a particular specialist appointed or reappointed to the National Health Service, finds regional hospital boards properly reluctant to choose anyone other than the best applicant for the job If the specialist has difficulty in establishing himself in this country, the difficulty can be even greater for general-duty officers who, though they may have been doing general practice at a high level, have usually been unable to secure National Health Service practices against the competition of younger men who have stayed here The gloom over our failure to reabsorb so many of our able people who have had the courage and enterprise to work abroad was epitomised in the statement of a speaker, two years ago, that he could not see how general-duty medical officers returning from Colonial service can fit in anywhere at any level in our medical services And this gloom seems as inspissated as ever, causing even the most sanguine to speak of this problem of medical resettlement as largely insoluble But are we not in fact dealing with a hangover rather than an incurable illness? If, as LAFITTE and SQUIRE [5] say, this country is shortly going to wake up and find

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[5] Lafitte F, Squire J R *ibid* Sept 3, 1960, p 538

Reviews of Books

The Problem of Acute Hypothermia

Editor P M STARKOV Translated from the Russian by R E HAMMOND Editor of English edition E NEIL, M D, professor of physiology, Middlesex Hospital Medical School London Pergamon Press 1960 Pp 329 70*s*

THIS book contains the results of many years research in Professor Starkov's department in Omsk There are twenty-eight articles by the fourteen workers concerned, and they are all physiological, though the hope is expressed that some of the conclusions may be put to practical use The subject titles alone make interesting reading, for, as might be expected, they imply a quite different approach to the physiology of hypothermia from that in the Western world, where much of the work has been planned pragmatically, according to the needs and problems of the operating-theatre, and not so much concern, perhaps, is felt about the basic differences between the body functions at normal temperature and those revealed during hypothermia Physiologists will therefore welcome the results of study on such fundamentals as cold effects on blood-flow in limbs and viscera, on the effects of direct cerebral cooling, and the use in hypothermia investigation of the values accorded by such familiar parameters as those of the heart-lung preparation, decerebrate cat, isolated rat uterus, and skeletal muscle Behaviour and conditioned reflexes in puppies and adult dogs are subjects of natural interest to Russian physiologists, and the response of these nervous patterns to hypothermia is the subject of one of Professor Starkov's own articles

The publishers regret that for speed and economy of production the text is in typescript photolithography, but the quality of the pages is even and good, and the content more than makes up for any deficiency The translation is commendably clear

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[2] *Hansard* July 28 1960 col 1869

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[4] See *Lancet* 1958 ii 1111

[5] Lafitte F Squire J R. *ibid* Sept. 3, 1960 p 538

Similarly the apparent risks of going abroad for a few years, on secondment or otherwise, may begin to bulk less large in the minds of candidates The Government are in favour of secondment from their own services here, and propose to have talks with representative bodies of employers " to seek their agreement to releasing staff on loan "—paying " in appropriate cases the differential between the terms of the overseas appointment and the local salary " If there are still senior members of the profession who are inclined to discourage their juniors from going abroad, we hope they will give thought to the white-paper's correct statement that service overseas affords " opportunities to do interesting work in a new environment, opportunities to exercise individual initiative and responsibility at an earlier age than is usual here, opportunities to develop personal qualities of self-reliance, leadership and adaptability arising from the wide variety of tasks to be undertaken opportunities to make an individual contribution to the development of a new country " Even more, perhaps, we hope they will read the remarkable review of the African situation, by Dr H S GEAR, which we publish this week Though GEAR credits colonialism with having given Africa a phase of social stability with a rising economy, and recognises that the main medical contribution has been, and still is, made by the official services, he is concerned mainly with the unofficial aspects of a system which hitherto has been continually nourished and refreshed from Europe " Medicine's true teachers and disciples give more to Africa," he says, " than medical care in a hospital or clinic ", and Western medicine should not overlook the need for this broader interpretation of its possible service " It should guide Africa to create people who are good doctors and nurses, but are also prepared to follow fearlessly the principles founded over many difficult generations in Europe and America "

Protein in Hyaline Membrane

THE chief component of the hyaline membrane found on histological examination of the lungs of premature infants who have died shortly after birth was once believed to be inspissated material derived from the amniotic fluid or vernix caseosa, and the term " vernix membrane " was used for some years[1] It now seems that a fundamental disorder of the pulmonary circulation plays a part in the formation of the membrane,[2] protein being extravasated from the pulmonary vessels into the neighbouring air-spaces and then forced by inspiration into a membrane lining the walls of these spaces

While most agree that the bulk of the membrane is composed of protein, there is still some difference of opinion as to its origin and nature LYNCH[3,4] initially suggested that the membrane represented a dried and concentrated secretion of the respiratory bronchioles and alveolar ducts Further work indicated that the membrane included hæmoglobin,[5] but the bulk of it was composed of fibrin[6,7] All these investigations reinforced the idea that the components of the membrane were derived from the blood-stream The various cardiovascular factors associated with hyaline-membrane formation were analysed by SHANKLIN[8] in a series of 335 premature infants He found that membrane formation was significantly more frequent in association with cardiac malformation that increased the pulmonary blood-flow The stages of the development of the pulmonary lesion were thought to be increased pulmonary blood-flow, left ventricular failure, pulmonary œdema, and membrane formation The possibility that maternal factors may play a part in the presumed circulatory disturbance has been investigated by COHEN et al,[9] whose work seems to indicate that membrane formation is commoner when the pregnancy has been complicated by toxæmia and especially by antepartum hæmorrhage From time to time it has been claimed that the frequency of hyaline membrane is increased in infants delivered by cæsarean section[10], but COHEN et al conclude that any such increase is limited to pregnancies where bleeding has occurred before delivery

The composition of hyaline membrane has been investigated by BUCKINGHAM and SOMMERS[11] They regard the structure as laminated acellular layers of eosinophilic material apposed to the walls of alveolar ducts, alveoli, and terminal bronchioles Ultraviolet microscopy showed that the material closely resembled plasma-protein or cell cytoplasm, in addition, some nucleoprotein was thought to be present Membranes produced experimentally by exposure of mice to oxygen had a similar composition The membranes thus seemed to comprise cytoplasmic material, hæmoglobin, polymerised fibrin, nucleoprotein, and mucoprotein These workers were impressed by degenerative changes in the bronchiolar epithelium, which they believe contribute to membrane formation Hyaline membrane may possibly be associated with hypersecretion of alveolar lining substance[12] which raises the question whether abnormal autonomic nervous stimulation enhances its formation, not only by promoting pulmonary œdema but also by increasing secretory activity in the terminal air-passages

Although highly specialised techniques have revealed fibrin in hyaline membrane, this does not stain for fibrin by ordinary histochemical methods It has been shown, however, that a hyaline material is formed when certain acid mucopolysaccharides react with plasma-proteins[13,14], and the possibility that a similar mechanism may operate in hyaline-membrane formation has been investigated by CARONE and SPECTOR,[15] who induced pulmonary œdema in rats by means of α-naphthyl thiourea and then introduced, by the endotracheal route, various substances including dextran sulphate, nasal mucus, meconium, and concentrated amniotic-fluid suspension. All these substances contain acid mucopolysaccharides, and all produced a membrane which had similar tinctorial properties to those of the membrane found in the human lung and which also failed to stain for fibrin. This suggests that, if hyaline membrane is indeed largely composed of fibrin, then this is probably in a polymerised form. Similar membranes were also produced when these acid mucopolysaccharides were introduced via the trachea together with plasma-protein in animals not previously given α-naphthyl thiourea.

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[1] Farber S , Wilson J L *Arch Path* 1932, 14, 437
[2] See *Lancet*, 1958 ii, 945
[3] Lynch, M J G , Mellor, L D *J Pediat* 1955, 47, 275
[4] Lynch M J G Mellor, L D *ibid* 1956, 48, 165
[5] Lynch, M J G , Mellor L D , Badgery, A R *ibid* p 602
[6] Gitlin D , Craig J M *Pediatrics* 1956, 17 64
[7] Van Breemen V L , Neustein, H B , Bruns, P D *Amer J Path* 1957, 33, 769
[8] Shanklin D R *Arch Path* 1959, 68 49
[9] Cohen M M , Weintraub, D H , Lilienfeld, A M *Pediatrics*, 1960, 26, 42
[10] See *Lancet*, 1960 i, 686
[11] Buckingham, S , Sommers, S C *Amer J Dis Child* 1960, 99, 216
[12] Pattle, R E *Proc roy Soc B* 1958, 148, 217
[13] Walton, K W *Brit J Pharmacol* 1954, 9, 1
[14] Pappas G D Ross M H , Thomas L *J exp Med* 1958, 107, 333
[15] Carone, F A , Spector, W G *J Path Bact* 1960, 80, 63

Even if the membrane is largely composed of fibrin, the reason for the chain of events leading up to fibrin precipitation in the lungs of some infants but not of others still has to be found. A possible clue is afforded by the work of LIEBERMAN.[16] As a result of preliminary studies he postulated that a deficiency of lung plasminogen-activator activity predisposed certain infants to hyaline-membrane formation. It could be objected that such a low enzyme activity might result from exhaustion of supply by the disease process itself[17], but any such doubt has been largely settled by LIEBERMAN and KELLOGG,[18] who have now evolved an improved technique for measuring tissue plasminogen-activator activity. They describe their findings in specimens obtained from 61 fœtuses and newborn infants, comprising 15 cases of hyaline membrane and 46 controls. All but 2 (4%) of the control series showed plasminogen-activator activity, and none showed any inhibitor activity. By contrast none of the 15 membrane cases showed activity when lung cubes were examined, but in 2 out of 11 cases homogenised tissue showed some activity. The remaining 9 cases studied by tissue homogenisation showed no activator activity, and in 8 of them evidence of inhibitor activity was found. These results confirm the previous observation of defective plasminogen-activator activity in association with hyaline membrane. The inhibitor of the enzyme, found in most of the affected lungs, may explain the lack of success which has attended the therapeutic use of fibrinolytic agents in affected babies. In a preliminary communication in our present issue Dr FLEMING and his associates at the National Naval Medical Center at Bethesda report apparent absence of plasminogen activator in the lungs of two men whose hyaline membrane followed "total body irradiation", and their findings in dogs were consistent with the view that irradiation produces a potent inhibitor of activation. LIEBERMAN and KELLOGG suggest that, in infants, the enzyme defect may be genetically determined.

SETNIKAR et al.[19] suggested that an alveolar transudate is an essential part of amniotic fluid. If this is so, a rich source of fibrin is contained in the fœtal lung, and, if fibrinolytic activity is defective or absent, fibrin deposits may gradually accumulate and form into membranes after the onset of respiration. Again, deficient proteolytic activity in the lung may interfere with the alveolar lining layer and so affect the surface tension in the pulmonary air-spaces. Such an increase in the surface-tension is thought to promote atelectasis.[20]

Although much work is being done on hyaline membrane, it is abundantly clear that our understanding of its formation is still deficient, and no effective remedy is in sight.

Troubled Families

"… the State's principal duty is to assist the family in carrying out its proper functions."

So say the Ingleby Committee whose report,[21] published last week, gives important and far-reaching advice on means of helping delinquent, disturbed, and neglected children under 17. Unfortunately cause and prevention did not enter into their terms of reference, but it is clear that the committee believed that the family and the relationships therein were the primary causes of later difficulties, whatever secondary influences may subsequently play a part—an emphasis which colours the recommendations throughout. The parents, as much as the disturbed child, need to alter their ways, and the committee have wisely regarded the child as a person to do things *round* rather than the patient or sinner to do things *to*.

Set up by the Home Secretary in 1956, the committee[22] record that at that time falling delinquency-rates and fewer maintenance and affiliation orders set a scene which, if not rosy, was at least hopeful. But since then this trend has been dramatically reversed, so that the Ingleby recommendations gain much in significance and will be given prompt Governmental scrutiny.

Considering first the ways in which help reaches the family, the report notes that inter-service rivalry has, in the past, impaired coordination and delayed the arrival of appropriately trained workers. Thus, while the committee welcome the help of almost any agency in bringing troubled families and children to notice, diagnosis and treatment require tactful handling and, very often, special skills not always found among those who concern themselves with the personal affairs of others. A reorganisation of the various family services is called for, with the establishment of an independent "family bureau" responsible only to the clerk to the local authority. Detailed consideration of local-government changes was beyond the committee's terms of reference and they urge further study of this matter, bearing in mind that differing local circumstances will call for flexibility in legislation designed to ensure efficient coordination. The report declares that "… there should be a general duty laid upon local authorities to prevent or forestall the suffering of children through neglect in their homes," and such authorities should be required to submit schemes for Ministerial approval The only bodies, the report goes on, with the power to bring a case before the courts should be the police and the local authority—a move, it seems, away from the sometimes harmful multiplicity of authorities bearing on the family This proposal, which removes such power from the National Society for the Prevention of Cruelty to Children, is likely to be a contentious one when debated in Parliament and elsewhere, but it is in tune with the legitimate trend towards professionalism in social work The days of the keen but untutored amateur are passing, and rightly so The reluctance of the committee to widen "juvenile liaison schemes", run by the police for cautioned offenders, springs from similar judgment

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[16] Lieberman J. *New Engl. J. Med.* 1959, 260, 619.
[17] See *Lancet*, 1959, i, 1234.
[18] Lieberman J., Kellogg, F. *New Engl. J. Med.* 1960, 262, 999.
[19] Setnikar I., Agostoni E., Taglietti A. *Proc. Soc. exp. Biol., N.Y.* 1959, 101, 842.
[20] Avery, M. E., Mead J. *Amer. J. Dis. Child.* 1959, 97, 517.
[21] Report of the Committee on Children and Young Persons. Cmnd. 1191. H.M. Stationery Office. Pp. 179. 8s.
[22] The members were Lord INGLEBY (chairman), Lady ADRIAN, Hon. Mrs P. L. AITKEN, Mr R. H. BLUNDELL, Mr DONALD FORD, Dr R. M. JACKSON, Mrs M. M. C. KEMBALL, Mr G. H. McCONNELL, Prof ALAN MONCRIEFF, Viscountess RIDLEY, Dr P. D. SCOTT, Mr G. A. WHEATLEY, Alderman D. T. WILLIAMS, and Mr J. P. WILSON.

Turning to jurisdiction, the committee note the trend, over the past century or so, towards separate provision under the criminal law for the young and, more and more, towards emphasis on the welfare of the child as the overriding concern This has led, the committee believe, to inconsistencies The principle of criminal responsibility and punishment for a certain act in a judicial setting has become uncertainly combined, by statute, with the obligation to serve the child's best and broadest interests Thus a trivial offence may, when the full appalling family circumstances become known to the court, lead to a seemingly severe and drastic disposal Furthermore, the widening of the court's function in 1908 and 1933 permitted a child to be sent to an approved school (a severe punishment very often) for the non-criminal offences of being "beyond control" or in need of "care or protection" In rethinking the place of juvenile courts the committee concluded cautiously that, however much a child may seem likely to benefit from interference by the State, compulsory intervention should not be applied except for the clearly defined and well-known reasons that already obtain The basic pattern of courts, too, with lay justices still finds favour with they committee, though they concede some virtues to the non-judicial tribunal

The trend away from criminal jurisdiction, however, should be urged forward, notably by raising the minimum age of criminal responsibility from 8 to 12 years, and later perhaps to 13 and 14 Though an important change of principle, the practice of the law would not be as much affected by this as might be imagined Already offending children under 8 may be brought before a court and dealt with as "beyond control" the court, under these proposals, will certainly not allow children to "get off", indeed by the greater thoroughness of the procedure, Society may expect better protection than before Children under 12 would no longer be charged with an offence, though if such were established (under the usual rules of evidence) it would count towards showing that the child was "in need of protection or discipline"—the new form of words empowering the court to take action The procedure would be swifter (cases would have to be tried within 28 days of detection, save in special circumstances) and more holistic, taking in the whole circumstances of the case The police and local authority would consult before proceedings began Though retaining the power to remove a child from home, the court would do so only when it was satisfied that his needs could not be somehow met without such action, and it would have the additional options of ordering attendance at an attendance centre or study in a remand home Fines and detention in detention centres would be withdrawn, but compensation to a maximum of £100 and/or costs could be demanded Committal to the care of a "fit person" would remain, and parent or guardian could be ordered to enter recognisance to exercise proper care and guardianship The court could also order supervision by a probation officer or other person for up to 3 years From 12 to 17 years procedure would be much as it is now, and the committee did not feel that the age-limit of 17 for juvenile courts should be raised, though they wondered whether a sort of half-way "youth court" for ages 17 to 20 or 21 might be examined further

The committee believe that the court needs to be much more active with the parents, summoning the attendance of both, bringing home to them their share of responsibility, and offering support where it is practicable The verdict of the court—so often a source of grievance—would be explained to them as far as possible Treatment, where compulsory, appears as punishment, and the committee admit that in practice it is impossible to distinguish between them On the other hand, parents would no longer have the right to bring children before the court as "beyond control", though appeal to the local authority might sometimes have the same effect if no other solution could be found Here, however, parents would not appear in the role of prosecutor, and the need for them to make damaging and rejecting statements towards the child in public would be reduced

The greater part (some 400 out of 550 paragraphs) of the report is a review of administrative detail arising partly from this survey and related to courts, sentences, and corrective institutions Few of the numerous recommendations will be disputed, nor are many of wide interest, important though they are Thus, an adequate course of training is recommended for all juvenile-court magistrates, who should usually be lay people, appointed between about 30 and 40 and retiring at 65 Better court-room accommodation for the children is needed, and the report calls for removal of all legal obstacles to accelerate the disposal of cases involving child witnesses, plus closer liaison with adult courts where necessary The committee approved the attendance-centre principle sufficiently to want to lower the minimum age to 10 and to widen the categories of offenders treated there For detention centres, however, a uniform 3-month sentence should take the place of the present sliding scale between 1 month and 6 (for under 17s only), and the committee are surely right in pressing for compulsory aftercare for a further 6 or 12 months

Approved schools are left much as they are, with a few hopeful calls for inter-school staff discussions and better psychiatric facilities, staff, and aftercare. Recent months have made it clear that all is far from well among the approved schools, but from present knowledge it is hard to see how the committee could go further than they have, timid though their recommendations seem. Finally, the committee want to extend somewhat the prosecution of cruel parents (to take in mental suffering short of actual derangement) and to increase the penalties to £100 or 6 months' imprisonment or both, though at the same time full use should be made of residential training and social aid.

In sum, these proposals do not seem to conflict with any of the many other Governmental reflections of recent years, and they all have it in common that the big problem in realising them is shortage of staff and money. (We have now heard from so many committees that a "survey of reports" might help to place the future of our social services in comprehensive perspective.) There is little of dynamite in the Ingleby recommendations. Juvenile-court organisation, in particular, has been left largely alone, to the disappointment, undoubtedly, of many. But the committee have reached a quite surprising degree of unanimity after their 4-year pilgrimage, and few who advocate sweeping changes have given such careful thought to the implications. These proposals, in the present state of therapeutic knowledge, are probably as far as we should go and must carry an excellent chance of early Parliamentary acceptance. Coming when voluntary acceptance of child and family guidance services is spreading and when compulsory treatment for "psychopaths" is becoming possible under the National Health Service we have now the foundations of an excellent service for children. The wisdom of this report cannot be in doubt, and the sooner it all happens, the better it will be for everyone.

Annotations

SOCRATES IN HARLEY STREET

Some two years ago, in a week when medical education was being considered at a formal conference in London, we printed a less orthodox discussion of the same problems in our peripatetic columns. It began:

> ALCIBIADES. Tell me, Socrates, how can we be sure that our doctors are well trained?
>
> SOCRATES. Do you think it right, Alcibiades, that we should say of a pudding that it is good or bad?
>
> ALCIBIADES. Certainly, Socrates.
>
> SOCRATES. It must be possible then to distinguish a good pudding from a bad one?

This learned ballon d'essai pleased readers, author and editor. Socrates was offered a column of his own, and throughout 1959 under the heading of "Dialogues of Today" he and his disciples debated in our columns some of the social and moral uncertainties of medicine and humanity, of our time and all times. Because the dialogues deal with problems which belong not only to medicine and not only to this country, we have reprinted them as a small book (with paper covers)[1] for the consideration of all who enjoy a good argument.

The dialogues range from birth control to death control, from ways of constituting a committee to the reasons for constituting a college, from the atomic bomb to less final methods of retirement. But if the matter is serious the manner is never heavy. No dogmatic conclusions are offered and the reader is left to continue the debate with his own friends—and perhaps with himself. The anonymous author admits that he has chosen the conversational form with provocative intent. His introductory quotation, borrowed from David Hume, another writer of dialogues, describes dialogue writing as peculiarly suitable for a topic which is obvious but important or for one which is so obscure and uncertain that the human reason can reach no fixed determination with regard to it. "Reasonable men," Hume adds, "may be allowed to differ, where no one can reasonably be positive. Opposite sentiments, even without any decision, afford an agreeable amusement." We hope that all our reasonable readers will find agreeable amusement with Socrates.

CHOLESTATIC VIRAL HEPATITIS

Even before the 1939–45 war it was recognised that a varying but small proportion of cases of epidemic viral hepatitis differed from typical cases in the difficulty with which they could be distinguished from cases of extrahepatic biliary obstruction.[1] Histologically the liver in such cases was characterised by the extreme mildness of the parenchymal lesions and their restricted focal distribution, the conspicuous features were multiple intralobular plugs of bile and moderate to severe infiltration of the portal tracts with both mononuclear cells and polymorphs. Hitherto deviation from the more usual pattern of the disease has not been satisfactorily explained.

Dubin et al.,[2] on the basis of their experience at a U.S. Army Hospital in the years 1951–53, suggest that the cholestatic form of hepatitis may be due to a variant of the usual virus. Their clinical material comprised 93 cases of viral hepatitis in which biopsy of the liver was undertaken within twenty-one days of the onset of jaundice. By means of clearly defined criteria these cases were classified into four types. Type A showed the diffuse necrosis with very slight bile stasis that is typical of classical viral hepatitis. Type B was similar, but intralobular plugs of bile indicated some added cholestasis. Type C was characterised by focal distribution of the parenchymal lesions and predominance of cholestasis. In type D parenchymal necrosis was negligible, the changes consisting almost entirely in bile stasis and cellular infiltration of the portal tracts. Patients with lesions of types A or B were regarded as having classical viral hepatitis, and those with lesions of types C or D as having the cholestatic form. When the cases were classified into serum hepatitis and infective hepatitis according to whether or not the patient had received a transfusion of blood or blood product in the six months preceding the appearance of jaundice, correlations appeared between serum hepatitis and the classical picture and between infective hepatitis and the cholestatic form This, however, was contrary to the results of all previous studies, and further analysis showed that the more probable correlation was between the variety of the disease and the area where it was contracted Thus of the 36 patients with serum hepatitis, of whom only 5 belonged to the cholestatic group, 30 had been transferred with their disease from the Far East, whereas of the 54 patients with infective hepatitis, of whom 21 belonged to the cholestatic group, only 8 were from the Far East and 46 were of local origin All 21 cases of cholestatic hepatitis occurred among the 46 local cases of infective hepatitis which suggests that the local epidemic virus had a remarkable predilection for inducing the cholestatic form of the disease Since no other factors, such as exposure to drugs or toxins, were apparently responsible for this distribution of the cholestatic form, Dubin et al feel justified in attributing it to some special property of the virus The even higher incidence of this form in the epidemic in Delhi described by Smetana[3] can be taken as evidence of widespread distribution of this variant of the infective-hepatitis virus

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[1] Socrates on the Health Service. 1960. London: The Lancet Ltd. Pp. 102. 5s. Obtainable from The Lancet, 7 Adam Street, London, W.C.2 (postage 5d.).

[1] Eppinger, E. Die Leberkrankheiten. Vienna, 1937.

[2] Dubin, I. N., Sullivan, B. H., LeGolvan, P. C., Murphy, L. C. *Amer. J. Med.* 1960, 29, 55.

THE GENE

IN a British Association Granada lecture delivered in London on Sept 27, Dr G W Beadle, professor of biology at the California Institute of Technology, surveyed mechanisms of heredity There seems to be no doubt that it is the cell nucleus that contains the primary hereditary message, the gene being the simplest unit of biological instruction, and some 10^4–10^6 of them being necessarily present in every human egg The only nuclear constituents of sufficient complexity to carry such a message are the proteins (linear polymers of some 20 different aminoacids) and the desoxyribonucleic acids (D N A) (linear polymers of only 4 different nucleotides) Evidence favouring D N A as the carrier arose initially from the demonstration that bacterial transforming factors (which cause a typical inherited change in some pneumococci) were composed almost entirely of D N A ,[4] but perhaps the most direct proof came from a study of a bacterial virus with inheritance characteristics known to be particulate These bacteriophages consist of a protein coat surrounding a core of D N A , and electron microscopy had suggested that the protein coat did not enter the cell during the process of infection The protein coat was therefore labelled with ^{15}N and the D N A with ^{32}P, and it was conclusively shown that only the D N A entered the cell Thus since these viruses have genes, and since only viral D N A entered, the viral genes must be D N A

The double-stranded D N A molecule,[5] where the sequence of nucleotide units in one strand automatically determines the complementary sequence of its partner, gave a clear indication of how accurate replication could occur provided that sufficient energy was available to separate the two strands by some sort of untwisting process[6] There is certainly enough D N A in a single human egg to carry all the required information, for about 10^{10} nucleotide units exist in the 46 chromosomes of the fertilised egg (ignoring the sex chromosomes), and such a number is probably sufficient to encode the contents of some 500 large books

The gene, then, can be thought of as a segment of the D N A chain, perhaps some 1000 nucleotide pairs in size, and the process whereby such a gene may direct the synthesis of an enzyme involves transferring the code to ribonucleic acid (R N A) (known to be associated with the chromosomes at certain times) by some kind of template system The nuclear R N A then passes to the cytoplasm, where it becomes incorporated into the microsomes Special segments of this R N A bind and activate specific aminoacids, which are thereby held in the correct order for the synthesis of the particular enzyme This type of synthesis probably occurs only when the enzyme substrate is present—so providing a necessary control to prevent every cell from undertaking all possible syntheses In this way differentiation may be controlled by environment A clear example of such genetic control of enzyme synthesis is the inherited condition of galactosæmia, where the patient wholly lacks the enzyme which changes galactose into a usable form

Mutations can be thought of as alterations of the sequence of nucleotides in the genic D N A either chemically (for example, nitrous acid changes D N A amino groups into hydroxyl groups and so upsets the hydrogen bonding on which accurate replication is thought to depend) or spontaneously under the influence of natural radiations Only occasionally, however, does such a mutation lead to an organism of increased reproductive fitness and so to a permanent evolutionary change

Professor Beadle ended by suggesting that paths now seem open, beginning with a universe of hydrogen, to an evolution through other elements, simple inorganic and then organic compounds, then through more complex organic systems to polynucleotides and proteins, the simple virus-like molecules, simple cellular systems, and finally to man himself

FROZEN BLOOD FOR TRANSFUSION

THE Cohn fractionator[1] is designed to separate individual half-litre units of blood into the component parts—red cells, platelets, and plasma—and to wash the red cells free from plasma It consists of a bowl centrifuge whose temperature can be kept constant, and whose bowl and associated containers can be sterilised Haynes et al have been using this machine for the long-term preservation of blood for transfusion The cells are washed with solutions containing up to 50% glycerin, then frozen at −80°C or −120°C, and after storage for 1 to 44 months thawed, deglycerinised, and reconstituted with an appropriate diluent According to requirements, the cells can be resuspended in saline, their own serum which has also been frozen, or 5% human albumin in an isotonic salt solution, to which can be added, as needed, buffers, globulin fractions, or components of clotting systems Of the red cells taken from the donor, 82% reach the recipient, and these seem to survive in his circulation as long as fresh cells Results have been so satisfactory that this frozen and reconstituted blood has been in routine use at the U S Naval Hospital in Chelsea, Mass , for more than a year So far over 1000 units have been administered without trouble, Haynes et al remark that febrile reactions have been remarkably few, and hepatitis has been absent

The cost of these benefits is considerable Rough costing suggests a figure of about £6 per unit, excluding building and heating, and a team of six workers using two fractionators can process only 200 units monthly Many London hospitals, dealing with 15,000–20,000 inpatients a year, may need over 500 units of blood in a month This would call for five fractionators and a team of twelve or fifteen, besides the existing staff of two technicians and a part-time doctor The cost of each bottle of blood for transfusion would rise from the present £1 25–1 5 to something like £6–7 Further, such hospitals use blood chiefly to treat unexpected hæmorrhage, relatively little blood is used for elective surgery or for the treatment of anæmia, so a large supply of fresh, or already reconstituted, blood would have to be kept on hand Now that the incidence of post-transfusional hepatitis has been reduced to 1 in about 800 transfusions, there seems to be little point in providing this expensive equipment for individual hospitals

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[3] Smetana, H F in Hepatitis Frontiers Boston 1957
[4] Avery, O T , McLeod, C M , McCarty, M *J exp Med* 1944, 79, 137
[5] See *Lancet*, 1959 ii 655
[6] Watson, J D Crick, F J C *Nature Lond* 1953, 171, 964

[1] Cohn, E J Proceedings of the fourth annual meeting of the American Association of Blood Banks, 1951
[2] Haynes L L , Tullis J L , Pyle, H M , Sproul, M T , Wallach, S , Turville, W C *J Amer med Ass* 1960, 173, 1657

On the other hand, there may be a case for setting up a few processing units for blood of unusual groups Very rare red cells such as -D-, could be reserved against need, and a moderate stock of blood of the less common groups which may be needed for extracorporeal circulations could be established In the past few months, because many regular donors have been on holiday, there has been a shortage of blood of all kinds,[3] which fortunately has led to nothing more serious than the postponement of elective operations for a week or two, it might be possible to store blood collected in the autumn, winter, and spring against the needs of the summer But such a project is bound to be expensive, and it is doubtful whether it would produce more benefits than would half the money spent on something else

SHINGLES AND CHICKENPOX

Wesselhoeft,[4] in delivering the sixteenth Charles Value Chapin oration, took the opportunity to review past and present ideas about the nature of chickenpox and shingles, and gathered into a valuable bibliography accounts of experiments and observations from many sources Those who thought that Weller and Coons [5] [6] in the laboratory, and Hope-Simpson [7] in the field, had convinced the medical profession of the unitary nature of varicella, however contracted, may be disappointed by the note of agnosticism on which he ended his address

The journals tend to give more space to rare than to common events, and this predominance may disturb the balance of a comprehensive review Rare occurrences are informative and must not be dismissed, but, still less, the common pattern of behaviour of a disease should not be overlooked There is a real danger of missing the wood for the trees, especially rare trees

The common relation between shingles and chickenpox is as follows Both can cause chickenpox in susceptible contacts, though the risk of this happening after contact with shingles is less than a third of its happening after contact with chickenpox. In either case the resultant disease is, by clinical, epidemiological, and virological criteria, ordinary chickenpox On the other hand, neither chickenpox nor shingles gives rise to an attack of shingles in contacts, whatever their previous history of either disease This is the usual pattern shorn of rare exceptions, and it determines the epidemiological behaviour found in practice—namely, that chickenpox appears in epidemics when aggregations of susceptible persons are effectively exposed to cases of chickenpox or shingles, but that shingles does not itself appear in epidemics and is independent of epidemics of chickenpox

For the " dualist " who holds that there is a distinction between ordinary and zoster-induced varicella there is a difficulty that seems never to have been adequately considered How far backwards must the antecedents of a case of chickenpox be traced before it can with certainty be classified as " ordinary " and not " zoster-induced "? Are ten generations of ancestry to be considered adequate evidence, or a hundred or a thousand? One observer traced back an outbreak for twelve months and classed it as " ordinary varicella " Had he, by pushing the inquiry still further into the past, found that the outbreak in fact stemmed from an original case of shingles, he would have been compelled to reclassify it as one of " zoster-induced varicella " Except in remote areas it is seldom possible to back-track in this way with any certitude, and, in such remote regions, outbreaks are commonly found to stem either from a local case of shingles or from a case of chickenpox imported from more crowded areas where further investigation of the lineage of the virus is difficult On all the evidence, it should surely be conceded that there is only one chickenpox, which can be caught either from another case of chickenpox or from a case of shingles

Much remains to be understood, foremost the nature of shingles itself If, as seems likely, it is due to the reactivation of latent chickenpox virus, where in the body is the latent remnant? Do all who have had chickenpox depend upon the survival of this latent brood for the preservation of their immunity? How is the symbiosis disturbed so that a harmony of maybe fifty years breaks down, the eruption develops in a dermatome, and infectious chickenpox virus escapes into the environment? On questions such as these light may be shed by the more unusual happenings, the anomalies and exceptions to the common pattern described above The least uncommon anomaly is the occurrence, usually in children, of a zoster during a primary attack of chickenpox—an apparent exception to the rule that contact with chickenpox does not give rise to shingles Much rarer are those cases in which shingles in an adult appears to have been caused by contact with another case of shingles or a case of chickenpox. How uncommon this is was shown by a prospective study of thousands of contacts of cases of chickenpox and shingles of whom not one developed shingles Nevertheless cases have occasionally been recorded in circumstances that make them very unlikely to be fortuitous Again there are a few records of attacks of zoster-induced varicella failing to protect against subsequent exposure to chickenpox All such rarities must find their explanation in a more complete understanding of the two diseases, but in the meantime they should not be allowed to obscure the picture which is already emerging

Even if some laboratory refinement should in the future discover a recognisable peculiarity of virus newly released by an attack of shingles from its intracellular confinement, the interesting observation would no more disturb the ætiological picture than a similar finding in spirochætes from late cases of syphilis would unsettle our present conception of that disease

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[3] See Graham-Stewart C. W *Lancet*, Aug. 20 1960 p 421
[4] Wesselhoeft C *R.I med J* 1957 40 357
[5] Weller T H *Proc Soc exp Biol* N Y 1953 83 340
[6] Weller T H. Coons A. H *ibid* 1954 86 789
[7] Hope-Simpson R. E. *Lancet* 1954 ii 1299

The Wider World

MEDICINE AND THE NEW AFRICA *

The Passing of Colonialism South of the Sahara

H S GEAR
M D, B Sc W'srand, D P H, D T M & H
FORMERLY CHAIRMAN, EXECUTIVE BOARD, WORLD HEALTH ORGANISATION, DEPUTY CHIEF HEALTH OFFICER, UNION OF SOUTH AFRICA

Africa south of the Sahara forms a unit of countries with many common features Because of early remoteness, climate, and disease, it was until lately isolated from Europe, and so lacks written history Its peoples—Bantu, Negro, Hamite—have many common physical and social characteristics It is the Africa of the tropics and semi-tropics, with desert, jungle, heat, and sun obtrusive - It has been the region of the world most affected by European colonialism It has had an evil name because of the men, especially those coming from temperate lands, who have been killed or disabled by its sicknesses

European influences were first brought to the continent by explorers, missionaries, traders, and prospectors In the 19th century the Colonial Powers, scrambling after them, launched tribal Africa into the Western way of life, and brought it precipitately into the material and technological world created by the Industrial Revolution Through the colonial agents of this world phenomenon, Africa was in time largely freed from the blight of tribal massacres, slavery, starvation, and epidemic disease

Today Africa is impatiently grasping the outward forms of sovereignty More than half her peoples will achieve political independence this year, and before the decade is well advanced the rest will almost certainly have followed Colonialism will then have vanished and new, and largely inexperienced, States will be struggling with the daunting social problems of emerging millions This fact, partly political though it may be, directly affects the future of medicine in Africa

The astonishing reduction in the amount of disease during the past 60 years has been possible because colonialism gave Africa a phase of social stability with a rising economy, and the whole paraphernalia of good central and local civil administration Western medicine had then its opportunity to prevent and cure disease " en masse "

Western ideas have moulded the form medicine has taken both in sovereign countries like the Union of South Africa and the Federation of Rhodesia and Nyasaland, as well as in the Colonial territories of Belgium, France, Portugal, and the United Kingdom In this medicine there has been a significant place for the medical missionary, the private practitioner, the medical professional association, the autonomous university with its medical school, and the public but unofficial research institution It has been a medical system constantly nourished and refreshed from the European home countries

But, though this European form of medicine has given a place to the non-governmental and the non-official, most medicine in Africa has a strong official character The hospital and clinic services of South Africa and the Federation and the general Colonial Services, despite their Western origin, are largely official and depend on Government funds for providing free or subsidised services

If the future held no other obstacles, the official nature of most of the developing African medical systems would create difficulties enough This official bias will be continued by most forms of external aid It makes uneasy those who would like to see the individual doctor and the non-official organisation claim a worthy place

Medicine, in a full sense, today only achieves results if there is an adequate community with law and order, efficient civil administration, good communications, and a sound economy In other words the good health of a community needs not only good doctors, but also well-run cities, villages, and country districts with sufficient food, pure water, efficient waste-disposal, proper housing, and all the other advantages of good government Inevitably the changing political and social scene in Africa will alter the future of medical and other public services

UNITED NATIONS AID

The New Africa is being moulded by external as well as internal forces The most important stimulus comes from the United Nations family, with the World Health Organisation as the agent responsible for health and medicine It is perhaps not fully realised how great a change is being wrought by the United Nations agencies, even though they are intergovernmental and not super-governmental organisations

Delegates from African States appear in ever-growing numbers in the councils of the world and many already have been effective office-bearers African regional and other offices already represent the U N Economic Commission for Africa, the U N Technical Assistance Administration, the Food and Agriculture Organisation, the World Health Organisation, and the U N Children's Fund Most of these directly or indirectly affect health programmes, and as a group are not insignificant in power and resources

A stream of people—consultants, technical experts, advisers, and others—are being directed by the U N group into Africa Another stream flows out carrying delegates, committee representatives, and postgraduate fellows and students

People moving in and out of Africa as part of its technical and scientific evolution are not a novelty But there is something very different about the flow sponsored by the United Nations family The volume is more impressive and it is directed to and from many more countries U N consultants and technical experts now working in Africa come not only from the United Kingdom, France, and the other colonial countries, but from North and South America, the whole of Europe, and several Asian countries The Africans travelling overseas for experience and training also visit a much wider range of countries

The technical aid in medical fields is massive It is gladly accepted by the new African States without the undue sensitivity they sometimes show to aid offered by individual foreign Governments As a result, the organisation of hospital services and clinics, and the training of doctors, nurses, and other staffs have been speeded up

A fundamental principle in this form of external technical aid is to be noted Since the United Nations system is official and intergovernmental, it works through national governmental services It is thus a force which quite properly creates and strengthens official and governmental services in the countries it helps It is supporting officialdom everywhere, and will increasingly do so in the future African medical and other services This is satisfactory provided non-governmental organisations and arrangements are not neglected

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* Based on a lecture delivered under the auspices of the Institute for the Study of Man in Africa, Johannesburg, on June 14, 1960

OTHER INTERGOVERNMENTAL ARRANGEMENTS

The passing of direct colonial control and the arrival of United Nations technical aid do not mean that the Colonial Powers have given up all responsibility for emerging Africa They are helping in the development of such things as general administrative services, universities, hospitals, rural clinics, research institutions, water-supplies, and roads Their hope is that if the new countries have sound public services the transfer of authority to peoples who, though politically active, are on the whole administratively and technically inexperienced will be smoother

It is not only the old Colonial countries which are eager to help the New Africa The Union of South Africa has often and officially stated that it wishes to draw on its own rich technical resources to help the rest of Africa Such help has already been given in many ways

Several South African scientists have visited other African countries, some have served as consultants, a few students from other territories have been trained in the Witwatersrand, Cape Town, and Durban Universities and medical schools, some research teams have worked on general African problems, and the South African Institute for Medical Research is used by many medical services as far away as the Sahara It is also part of several international scientific networks—e g , in virus diseases, spirochætal infections, bilharziasis, malaria, and so on

However, it is doubtful if South Africa yet plays a part proportionate to her technical resources Compared with the many scientists and doctors working in the New Africa who have come from Britain, France, and other European countries, or with the hundreds of undergraduate and postgraduate African students who flock to other medical centres, South Africa seems inactive Yet unless she vigorously develops this two-way exchange of medical scientists and students, her own medicine and science may languish as an international or African force

A more recent feature of intergovernmental technical aid to Africa is the bilateral governmental system Its first great advocate was the United States of America, and Africa has benefited liberally American medical missions are important now in many African states, and there is a steady stream of African students to the great medical and public-health schools of the United States She is keen, too, to cooperate with local groups in research into the many tropical and other diseases which are still difficult to control or treat such as bilharziasis, malnutrition, and many parasitic conditions

But the American bilateral programmes are having some unexpected imitators The Communist countries are already at work in many fields, including medicine, and it is probable that the Chinese will also join in sending technical experts and attracting fellows and students from the African States

NON-GOVERNMENTAL INFLUENCES

The pioneers of Western medicine in Africa, as elsewhere, were not officials but private doctors, and the medical missionary was the pioneer of the pioneers For a hundred years these courageous and selfless people have been among the great medical and social liberators of Africa Their work, generous and independent, goes on Today it is perhaps again critical If tolerated in the new countries, these societies could be a valuable instrument in continuing the spirit and practice of personal and non-official medicine of the best type

It was earlier inevitable, in tropical and tribal Africa, for the Colonial Powers to break the shackles of epidemic and endemic disease by introducing modern medicine through official services So, with the important exceptions of the larger European communities, the private doctor has not been a force

Again, with the exception of South Africa and Southern Rhodesia, medical and nursing professional associations have had an insignificant influence on medical and health policies in Africa compared with the part they have played in Europe and America The professions are generally a sound influence on official ministries, for in considering national health problems they usually hold more than a narrow professional view They contribute wisdom and experience and usually add to the maturity of the community It is, therefore, unfortunate that strong professional associations with a backbone of independent doctors seem unlikely to develop in the newer African States

Yet, paradoxically, one of the dangers threatening medicine in Africa is the private doctor who abandons the ethical code of his profession The charlatan in Africa is already playing on the credulity of the naive and superstitious He may be witch-doctor, masquerading doctor, or qualified practitioner prostituting his calling The new States, therefore, have a clear responsibility to protect their people from exploitation But the State will not succeed in this aim without a medical profession of the highest integrity keen to keep its own house in order

Industry has also contributed to African medicine Most large industrial organisations have acknowledged their obligation to protect the health of their communities In the gold, copper, and trading industries of South Africa, the Rhodesias, the Congo, and West Africa hundreds of thousands of workers are given health and good physique and learn much about keeping themselves fit during the years of their employment Much of this knowledge diffuses into the kraals and villages Hence the position of industry in the new States is of concern to medicine If they accept that private industry can contribute to the economy, this will open a useful opportunity for non-governmental medicine

Another non-governmental agent which could do immeasurable good for medicine in the New Africa is the large philanthropic or public Foundation In Africa the Rockefeller and other American foundations have been joined by the Nuffield Foundation, whose support for the establishment of a vigorous and modern medical school in Salisbury is likely to be one of the germinal events in Central African medicine As Africa changes from colonialism, the great Foundations, both American and British, will have an opportunity of service greater than in the past They are altruistic, objective, generous, and free of politics and bureaucracy They thus can balance the help coming to Africa from the intergovernmental agencies—multilateral or bilateral—with the best type of non-governmental support It will be unfortunate if the new States are unwilling to invite the Foundations to help in the large new medical, technical, and social programmes for which they will soon be responsible

A final example of non-governmental health and medicine is the voluntary organisation In South Africa and the Rhodesias, and to a lesser extent in the Colonial Territories, such bodies have been valuable, and it is to be hoped that the New Africa will encourage the work of voluntary groups, particularly in child and maternal health, first-aid, accident prevention, and social welfare But many circumstances are against them, especially if the new States loosen their Western relationships

SOCIAL TRANSFORMATION

The New Africa to which medicine must adjust itself is as much a product of social, including economic change as of the more obvious political movements These social changes—in such things as education, economy, agriculture, industry, science, and communications, and in religion—have been accelerated by the results of Western medicine The reduction of pestilence, as much as the control of famine and tribal warfare and the abolition of slavery, launched the African social revolution Now, along with the present political and nationalistic movements, these social forces are influencing the future setting for African health and medicine Indeed the replacement of the social customs of tribal Africa, by something modelled on, or influenced by, external ideas and examples, is happening too rapidly for medicine and the other social services to keep pace Even if these social forces are not diverted or delayed by political troubles, medicine in the New Africa will still have to face problems very different from the old

One is already ominous—the growth of population Released from the old checks of slavery, starvation, tribal war, and preventable disease, the annual rate of increase in some territories is already 3% People are migrating into the towns and factories, and large urban and industrial populations may place an unbearable demand on public, including medical, services The witch-doctor is no longer supreme Old fears have gone, so that hospitals and clinics are being swamped, and overworked doctors and nurses are driven to exhaustion Africa, like most other developing countries, has too many ugly and squalid towns and villages, and yet their inhabitants increase relentlessly to make slums more depressing and dangerous Only watchful sanitary administration and good fortune seem to explain the relative absence hitherto of serious disease

Another feature of the social transformation of importance to the medical reformer is the growing emancipation of the African women In much of Bantu society women still lack freedom and are only slowly training as midwives, nurses, health visitors, or teachers Sufficiently educated girls are deplorably few to meet the urgent demands of nursing and teaching

CHANGING PATTERN OF DISEASE AND DISABILITY

Africa's reputation has not yet recovered from the casualties among those who in earlier days came to explore, trade, or fight Portuguese missions defeated by fever, Mungo Park's expedition ending in disaster, Dutch, Danish, French, and British trading-posts on the West and East coasts enlarging their cemeteries daily, the decimation by typhoid and dysentery of the South African, and by the malaria and dysentery of the East African campaigns of the first world war—these and many more gave a sinister name to the climate and disease of Africa

Before medical science unravelled the maze of tropical disease, the hazards of Africa seemed to lie in its malignant climate Sun, swamp, heat, miasma—all were accused However, recognition of the true situation has seen the dramatic conquest of most of Africa's pestilential and tropical diseases Not only is the indigenous African population doubling itself every 30–40 years, but European families are living happily and healthily even in such dreaded areas as the West Coast and the Central African Valleys If one of the 18th or 19th-century Europeans returned, he would perhaps be chiefly amazed by the contempt of the moderns for the huge pith helmet, red spinal pad, and abdominal or cholera belt which he considered an essential protection against the baleful African sun and climate

Today we have gone a long way towards separating the climatic and environmental from the communicable and nutritional factors in the cause of African disease The greatest triumphs were the discovery of the causes and methods of treatment and control of the tropical fevers The devastating epidemic and endemic diseases of previous centuries are now cowed Yellow fever, malaria, sleeping-sickness, smallpox, dengue, yaws, and many more are shadows of their former selves The blame placed on tropical and African climate is now known to have been much exaggerated Now we know that an efficient sanitary system and a good diet can make nearly all Africa tolerable and healthy

Formerly nearly all the dangers to life lay in communicable disease carried by insects or infected food or water Climate was indirectly responsible in that it gave these diseases the medium for their propagation With disease reduced or eliminated, tropical climates become themselves less fearsome, if still uncomfortable Today we know much about the direct effects of sunlight, heat, and humidity Unpleasant though extremes of these may be, their effects can be borne more tolerably by applying the present knowledge of the human body's capacity for acclimatisation and adjustment Much of this work was shown on the Witwatersrand—e g , the regime of adjustment to work, environment, heat, and humidity applied in the mines The human power of physiological adaptation, combined with modern housing and work places, and, if necessary, air-conditioning, is radically changing the medical view of the future capacity of Africa to support healthy human populations even in its more fearsome desert and jungle regions

With the astonishing decline of the pestilences a new pattern of diseases is appearing Some of these diseases have always existed but were overshadowed Others seem to be truly new, or much more virulent Others are a product of social change

Examples of diseases now more prominent by contrast are malnutrition and some of the dysenteries Mass famine is now rarely seen, but protein malnutrition has lately been recognised as widespread Infantile diarrhœa persists as a serious public-health hazard

A group of diseases partly old and previous unrecognised, and perhaps partly new or more virulent, is those caused by viruses Besides such well-known viruses as those of poliomyelitis, influenza, and trachoma, a whole host of new agents has been found in Africa Much of this research has been done in the South African Poliomyelitis Foundation supported by a team from the Rockefeller Foundation

Two examples of conditions aggravated by the stresses in a society shifting from the pastoral to the modern are tuberculosis and industrial disease Unfortunately tuberculosis is increasing in nearly all African territories, especially in the town and labouring groups The story of industrial expansion in other continents is unhappily repeated Again, increasingly as the New Africa becomes industrialised, the problems of disease in mines and factories will arise, especially if the vigilance of the national health and labour administrations slackens

Modern life is not only putting people into factories and towns, it is altering the agricultural scene More and more large-scale agriculture in Africa is dependent upon irrigation This is spreading bilharziasis and making the control of its snail vector more difficult Several other parasitic worm diseases and intestinal infections continue to cause much sickness and inefficiency throughout tropical areas Their reduction must await improved sanitary services and higher personal standards of cleanliness

In the new pattern of disease one feature is becoming more and more striking—accidents. Even in remote regions of Africa accidental injuries are serious. Every new road brings an almost incredible number of car and lorry fatalities and cripplings. In New Africa, as in the rest of the world, the accident of the home, road, and factory is killing and maiming people and filling hospitals in ever larger numbers.

As the acute diseases recede and as the chance of living longer in a modern world increases, the so-called chronic degenerative conditions obtrude themselves. Here, too, Africa shows signs of copying the world design. Whatever may be the full story of their causes and associations the melancholy record in more and more countries is of death and disability from heart and kidney disease, nerve degenerations, and malignant disease. The mental afflictions, too, will probably be more obvious in the future Africa.

WHAT PATTERN FOR MEDICINE?

The speed and confusion of events are unfavourable to prophecy, but once the transition to sovereignty is achieved and a new African political condition is created, what will be the philosophy and form of its medicine?

In an immediate technical sense there will be enormous tasks to shoulder. The prospects of rewarding careers will lie before the new African doctors and nurses—suffering to be relieved, premature mortality to be challenged, fuller and healthier lives to be sought for the growing millions. They will also have an enviable opportunity to probe many remaining mysteries in disease. They will be the privileged observers of the whole gigantic phenomenon of a people being changed by social pressure to accept new ways of life. Such tantalising questions as the effects of climate and environment on energy, mental capacity, physiological efficiency will be theirs to study. Medicine in the New Africa will be rich in obligation and in opportunity for research.

Public-health and preventive medical measures to meet the challenge will only be effective, indeed possible, if the general administration is competent. But even assuming that no disastrous weakness appears in the public-health organisations of the New Africa, its future medical philosophy is still uncertain.

Medicine at its best is something finer than an exercise of technical skill. In the medicine being introduced into Africa and other developing regions this broader duty is too often neglected. Yet here the need is more desperate than in the older lands where all upbringing supports understanding of such social responsibilities. The culture and civilisation which have produced modern medicine, and of which it can be a noble component, are also essential in the new countries if they are to gain completely. Medicine's true teachers and disciples give more to Africa than medical care in a hospital or clinic. Their integrity and philosophy are a demonstration of the goodness to be found in their culture. This is necessary if the struggling new African medicine is to be something more than a mere materialistic technique or rival to tribal witchcraft, which could easily revive under a cloak of African nationalism.

Western medicine in helping Africa should not overlook the need for this broader interpretation of its possible service. It should guide Africa to create people who are good doctors and nurses, but are also prepared to follow fearlessly the principles founded over many difficult generations in Europe and America. This responsibility will be more onerous in New Africa than in the older settled communities of Europe and America. But the future African doctor, by being a man of integrity and principle, will increase the stability of his country and the respect it will earn in the world.

Special Articles

THE MINISTER ON THE HEALTH SERVICE

MR ENOCH POWELL, Minister of Health, reviewed the structure of the National Health Service in an address to a joint meeting of the English and Welsh Executive Councils Associations at Llandudno on Oct. 27. He said:

"The National Health Service, by its very nature as a comprehensive State service, holds out dangers and possibilities of harm as well as opportunities and possibilities for good. We can never wholly eliminate the risks and be left with only the opportunities. What we have to do is to discern as clearly as possible where those risks lurk and what they are. We shall then be in the best position to counteract and minimise them."

The service was the channel through which flowed the overwhelmingly large proportion of our national income which we devoted to the care of health and the treatment of the sick. The fraction so devoted had not, on average, been much larger during the last decade than it was twenty years earlier—though, of course, the national income itself had been larger and so, consequently, had been the absolute amount of resources devoted to medical care. One thing was certain: as our national income continued to rise, the volume of effort and resources devoted to health would rise. Another thing, too, was certain—that with the inevitable changes in the texture of society and in the content of medical knowledge and theory, the nature of the resources and the application of the effort devoted to health would also alter. In any given state of society and medical knowledge there was an ideal application of the available resources which would yield the greatest harvest in terms of health, wellbeing, comfort, reassurance—in short, of happiness. We should never quite attain this ideal, but we ought always to be tending towards it, and success or failure in doing so depended on the nature and the functioning of the channels through which the available resources flowed. Mr Powell continued:

"It is in this context that a comprehensive State service has its dangers. In such a service responsibility is inevitably centralised—in the Minister answerable in Parliament. Because responsibility is centralised, so, in large measure, must be decision, since responsibility implies the power to take the decisions for which one is answerable. This in turn implies an administrative machine which will link all the parts together and secure conformity with the central policy and decisions. Now, all this brings with it a great danger—that of rigidity. Policies which are formed centrally and executed administratively are bound to be slower to change and less adaptable to alterations of circumstance and demand than if responsibility were diffused and decisions were independent. The great machine is bound to have a one-track mind, to be cumbrous and unresponsive, to abhor variations, to be insensitive to the world around it.

"These disadvantages apply anywhere, but in the field of health and medical care they can be specially dangerous. Here is a field in which it is the individual mind, the local experiment, even the chance observation, which bring about the great advances. The man or woman who is (as we say) before his time, at whom officialdom is bound to look askance, whom contemporaries treat as an oddity or a nuisance, turns out to be the pioneer, doing the work which determines the direction of future development These people need an environment in which they have opportunity, even encouragement, certainly not repression But how is the machine to know them when it sees them?”

Not only the methods of giving medical care, but the character of the need for it were constantly changing Post-war legislation and planning for all the welfare services reflected the conditions of the pre-war world for it had nothing else to go on They were trying now to assess the revolution of the 1950s, but it might be far into the 1970s before they could adjust the machinery to take account of it This conflict between the characteristics of a comprehensive State service and the facts of social change and medical progress could never be fully resolved, for it was inherent But by recognising it, there was much they could do to limit and counteract its dangers

Those who framed and hammered out the National Health Service were not unconscious of the dangers, and they deliberately embodied in its structure elements of independence, both lay and professional, to be a counterpoise The contractual status of the general practitioners, dentists, and opticians, the separate representation of the doctors and other professions in the structure of the hospital and executive council services, the power and authority of the professional colleges and associations—these might seem to have a fine old English illogicality in a State service “But a wise Minister of Health will see in them not hindrances but safeguards to the soundness of his work, and in all that I do or seek to do I shall be as jealous of the independence of the professions as they are themselves,” said Mr Powell

But all these built-in counterpoises in the structure of the National Health Service to the dangers of the great machine would not be sufficient if the great machine itself were all “The National Health Service is intended to be comprehensive, it is not in my view intended to be exclusive,” went on Mr Powell “For the service’s own sake, I attach the highest value to the fact that medical service and care is also available outside it and that completely independent organisations exist in the field, to support and conduct research, to study and criticise, to supplement, assist, and (why not?) overlap the services provided by authority of Parliament” He welcomed the flexibility and spontaneity which these other channels bring to the nation’s provision for health

Mr Powell recognised three trends in the modern approach to health and medical care (1) the growth of community care and aftercare of the sick, “which takes off the hospitals work which can be done more effectively and more beneficially outside them”, (2) the development of preventive and remedial measures which will prevent admission to hospital or lengthy treatment there, and (3) the more intensive and efficient use of hospital accommodation, expressing itself in higher turnover of patients and lower ratio of beds to population In two of these three the initiative in development lay with the local authorities, and if the new trends were to find full expression, the biggest expansion within the health service in the next decade would have to come on the side of local government One should note finally that as the link between the three trends is, from one point of view, the patient as an individual human being, so the link from another point of view is the friend and adviser of the patient as an individual human being—namely, the general practitioner

Turning to finance, Mr Powell declared that the financial structure of the National Health Service could not have been devised more effectually if the object had been to put the three main elements into watertight, non-communicating compartments There were in fact three separate financial systems, and consequently the interrelation between developments and decisions in each of the three fields was virtually impossible to express in the clear financial terms which would so much help administration and public understanding “However, I must say bluntly that a major reform in the financial structure of the National Health Service is farther off at present than the eye of a politician can see We must work with the structure we have got, and I shall not be content until I can see a long-term picture in which the development of the hospital service is dovetailed with the development of the local-authority services, and the future function of the family practitioner is related to both”

Dialogues of Today

SOCRATES, THIS IS YOUR LIFE!

Haemon Come in, Socrates, and don’t be surprised to see so many people We know that you are becoming an author yourself for the first time, so we thought we would like to congratulate you Socrates, this is your life!

Socrates It is true, Haemon, that I am no longer to be dependent upon Plato and Xenophon for an account of my words, but I am no author any ideas to be found in my conversations are contributed by those with whom I talk I am only a midwife, delivering other people of their ideas

Haemon Come in, Apollodorus, and tell us how you first met Socrates

Socrates Welcome Apollodorus! What have you been doing today?

Apollodorus I have been in court arguing as to whether or not certain words are obscene

Socrates Is there any more important question?

Apollodorus I should hardly have called it important, Socrates

Socrates But tell me, is not obscenity sometimes a kind of swearing?

Apollodorus Sometimes it is

Socrates And when men swear do they not use words, which are held sacred, in a way which is considered blasphemous?

Apollodorus Certainly

Socrates It would seem then that if we are to decide why words are obscene we must also consider what makes words sacred, and we can hardly do that without asking what is sacred, and why it is so So you see why I said that the nature of obscenity is a most important question But, tell me, is there any characteristic of the obscene words themselves which distinguishes them from other words?

Apollodorus I don’t know of any

Socrates Are they not all short words, usually of one syllable?

Apollodorus I suppose that is true, but surely it is not the form of the word but the meaning which renders it obscene

Socrates Surely not, Apollodorus, for if instead of a word of four letters you use an equivalent one of four syllables, the feelings of your hearer will be quite different, although the meaning is the same Does it not seem to you that a short word contains all its energy in a small space and at high tension, and at once conveys to us a physical reality, whereas a word of four syllables carries its energy at low tension, and so conveys a meaning which is emotionally diluted, and makes far less impression on the feelings ?

HAEMON Thank you Apollodorus! Now here is Analyticus

SOCRATES It is appropriate that you should have come just now Analyticus, when we are talking about obscenity, for are there not many people who think all your writings obscene, even though you use many words of more than four syllables ?

ANALYTICUS Yes, indeed, Socrates, but when I am called a corrupter of youth I console myself with the fact that they call you the same.

SOCRATES Tell us why you think some words are obscene.

ANALYTICUS I think the form of the word is only one factor, important though it is A word may transmit emotion forcibly, but the emotion is related to the thing signified If some things were not sacred swearing would lose its point, but so it would if it were not considered reprehensible, and it is reprehensible only because some things are sacred. People sometimes speak of obscenity as animalism, but that is just what it is not Animals alone are innocent of obscenity Obscenity implies a sense of guilt. If you never swear you are either perfectly balanced or too conscious of your own guilt

HAEMON Here is Eryximachus

SOCRATES Welcome, Eryximachus, for there is no one more fitted than you to explain to us the nature of obscenity, since no one behaves more shamelessly than you.

ERYXIMACHUS How is that, Socrates ?

SOCRATES Do you not discuss with your patients matters which they would be ashamed to talk about with anyone but a doctor, and when you examine them do you not insist that they should conceal nothing which their modesty makes them conceal from others ? And in all this do either you or your patients feel any shame ?

ERYXIMACHUS But there is nothing obscene in all that, Socrates, for modesty is a matter of convention and shame does not arise in the relation between doctor and patient

SOCRATES It is the same with me, for I am not only a midwife who delivers men of their ideas, I am also a physician who seeks to examine their thoughts in all their nakedness and a surgeon who practises the orthopædics of the mind And it is my aim to examine men's words and to persuade them to let them be examined in the same spirit of truth with which Eryximachus examines their bodies

HAEMON I am sure we all wish your book the success it deserves Socrates, master of words, this is

XANTHIPPE (*marching firmly into the room*) your wife! I'll give you words! Was there ever such a man ? He hasn't slept for two nights, yet here he is talking about words And he drinks twice as much as anyone else without getting drunk, and sleeps out of doors wherever he finds himself, without even a blanket. But what does any of you care so long as you can get him to discuss philosophy ? I'll give you a bit of philosophy Where do his words come from ? Where does his life come from ? Ultimately from my kitchen Think that one out, all of you! Come on, Socrates, we're going home

(*They go*)

The Widdicombe File

LXVI.—THE DIVISION OF PATHOLOGISTS

DEAR PETER,

I thought your letter* was a very sound and moderate statement of the case—as stated by a supporter of a Faculty with the Physicians Of course you were trying to be impartial, just as every decent pathologist tries to be when he rehearses the arguments, but it is just impossible. The only man who can be truly impartial is the man who does not care one way or the other, and he will not trouble to rehearse the arguments at all That presidential address which you rightly describe as statesmanlike was, I know, meant to be impartial, but to me the final section seems to emphasise the advantages of a Faculty and the disadvantages of a College

You have recited some of the arguments for and against both sides, and I would like to review some of them as a supporter of the College You quote the argument that the establishment of a College "would be a cripplingly expensive undertaking", but this is obviously untrue unless we develop delusions of grandeur and try to obtain in a few years the sort of accommodation which other colleges have taken centuries to build up The independent Faculty of Radiologists, which is doing for radiology what a College would be trying to do for pathology in its early years, is able to exist simply and economically, and so could we You quote the argument that any examination set up by the College would take many years to achieve recognition, but what is the evidence to support this view ? There is after all no really satisfactory examination at present for would-be consultant clinical pathologists, and if a College of Pathologists provides a good one I can see no reason why it should not quickly become accepted

As for the College of Physicians, it is difficult to consider it as anything but what the name implies, even though I agree that it is not exclusive, and accept that out of every 100 "active Fellows" there are about 11 administrators, 9 pathologists, 6 academic pharmacologists, physiologists, or research-workers, 2 radiologists, and an obstetrician It could, of course, cease to be primarily a physician's college, but is that the wish of most physicians ? I would agree that most clinical pathologists, if they had taken up any other specialty, would probably have wished to become physicians rather than surgeons or obstetricians But clinical pathologists are still not physicians except in so far as a few hæmatologists have their own patients, and although we certainly must remain *clinical* I see no reason why we should enter into closer relations with the physicians than with any other special group of doctors

"If we were all certain that we could trust the Physicians", you say, "I think few would hesitate to accept their offer" I think you miss the point This is not a matter of trust, but a matter of intelligent anticipation of the possibility that the interests of physicians may not always coincide with those of pathologists If they do, well and good, but suppose they do not ? You say that "if, after an honest trial we found ourselves unable to agree with them, nothing could stop the faculty then splitting off" I think you overlook the fact that the Faculty would be a creation of the College of Physicians, not of pathologists, and it could hardly split off as a body unless the parent college chose to abolish the Faculty Are you prepared to envisage a future situation when a body of dissatisfied pathologists has to try to set up an independent college in opposition to an established faculty? Then indeed the "dissensions and bankruptcy" of which you warn us might well become a reality

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* We printed this letter from the File on Oct 22.—ED L

Our seniors often tell us that there is no advantage to them from either course, and that they are only concerned to provide for the younger pathologists in whose hands the future lies At the same time they tend, perhaps, to ignore the experience of most of those who discuss such matters with these younger pathologists, and find that they are mostly in favour of a College The young men do not seem to be afraid of starting in a small way provided that they can feel genuinely independent and not a sort of appendage to another college Their "image" of pathology is of a subject which is of real importance in its own right and which can therefore expect its own separate and individual organisation

If we are to build surely for the future, independence is the only safe choice When I have reached retiring age, I do not want my juniors to be able to say to me "You and your colleagues made a fine mess of things in 1960 Here we are stuck in the College of Physicians where we are not really happy, but it will be very difficult to break away now If you had only made the effort to form a College it would be well established by now Did you *have* to choose the easy way? Couldn't you see just a little way in front of your noses?"

Yours,

G G

Symposium

TICK-BORNE ENCEPHALITIS VIRUSES

FROM A CORRESPONDENT

The Institute of Virology of the Czechoslovak Academy of Sciences acted as hosts to virologists from eleven different countries during a four-day symposium last month on the biology of viruses of the tick-borne encephalitis complex The meetings were held in delightful surroundings at the House of Scientists at Smolenice, near Bratislava Representatives from almost all the major groups working on this subject were present, and the symposium provided an unusual opportunity for workers from many different disciplines to pool information and exchange ideas in a common approach In Britain, human infections with louping-ill virus do not present a serious public-health problem, but in Central Europe, Scandinavia, U S S R, and India viruses of the tick-borne encephalitis group are a serious menace The recent recognition of human infections with viruses of this group in Canada[1,2] and the U S A[3] extends the area in which these viruses are known

Dr J Casals (New York) showed how the tick-borne viruses were placed with yellow fever and some twenty other arthropod-borne viruses into the serological group B on the basis of antigenic relationships In the past, the tick-borne encephalitis viruses have been considered a homogeneous group in spite of wide differences in the disease patterns they produced in different parts of the world Dr D H Clarke (New York) showed that they could be divided into six antigenic subgroups on the basis of hæmagglutination inhibition tests with absorbed sera and by agar-gel precipitin tests The six subgroups were represented by the classical far-eastern Russian spring-summer encephalitis (R S S E), louping ill, Omsk hæmorrhagic fever, Kyasanur Forest disease,[4] Malayan tick-borne Langat virus, and Central European tick-borne encephalitis which included Czechoslovakian, Austrian, Finnish, Polish, Swedish, and Yugoslavian strains, as well as strains from European U S S R The recently described North American Powassan virus had not yet been examined by these techniques These antigenic differences were important because they explained the reported failure of R S S E vaccine to protect humans (Dr P N Bhatt, Poona) or mice (Dr L Daneš, Prague) against infection with the virus of Kyasanur Forest disease

As in other branches of virology, tissue-culture techniques were gradually replacing older methods for the titration of viruses and for the detection of neutralising antibodies The use of a plaque technique for the titration of tick-borne encephalitis viruses was described by Dr J S Porterfield (London) and was applied by Dr V Mayer, Dr J Zavadá, and Dr R Škoda (Bratislava) to Central European strains Dr Bhatt reported that chick fibroblast cultures were as satisfactory as mice for the primary isolation of Kyasanur Forest disease virus Czechoslovak workers preferred a two-stage process—primary isolation in tissue-culture cells which were later shown to be infected by virtue of their resistance to a challenge virus Neutralising antibodies were detected by a metabolic inhibition test carried out in Hela cells (Dr H Líbiková and Dr J Vilček, Bratislava), by plaque inhibition (Dr J S Porterfield, London), or by the direct inhibition of cytopathic effect in Hela cells (Dr E Molnar, Budapest) or in pig kidney cells (Dr D Málková, Dr Z Marhoul, Dr V Fraňková, and Dr V Černy, Prague)

Vaccines derived from formalinised mouse brain had been used for many years in the U S S R (Prof E N Levkovich, Moscow, Prof A A Smorodinstev, and Dr V I Ilyenko, Leningrad) and formalin-inactivated louping-ill vaccine had been used to protect laboratory personnel (Dr D G ff Edward, Beckenham) and domestic animals (Dr D Blascovic and others, Bratislava) Attempts at producing a vaccine from virus grown in tissue culture were reported from Prague (Dr R Benda and Dr Danes), from Budapest (Dr E Molnar), and from the U S S R The major difficulty was to guarantee complete destruction of infectivity without at the same time reducing the antigenicity of the vaccine There were many parallels with the poliomyelitis vaccine problems A further important factor reported by Dr G D Zasukhina (Moscow) was that virus grown in tissue culture with a deficient medium was less antigenic than virus grown in a rich medium

The maintenance of the tick-borne viruses in Nature is still not completely understood The course of infection in an experimental animal, the laboratory mouse, was studied by Dr P Albrecht (Bratislava) in an elegant series of experiments based on the use of fluorescent antibody techniques Other animals which may be infected in Nature include bats and lizards (Dr J Rehácèk, Dr J Nosek, and Dr M Grešiková, Bratislava), domestic ducks (Dr E Ernek, Bratislava), and coots (Prof H A E van Tongeren, Leiden) Much remains to be learned about the natural history of this group of viruses Although the great majority of infections are transmitted by the bites of infected ticks, mechanical transmission by mosquitoes (Dr Z Zotowski and Dr Z Wroblewska-Mularczykowa, Warsaw) or fleas (Dr K Heyberger, Dr A Smetana, and Dr B Rosicky, Prague) may play some small part in the local spread of infection, and infection by the ingestion of milk from infected goats, sheep, and cattle is now well established The many factors which influence the natural history of viruses of the tick-borne encephalitis complex were ably reviewed by Dr T H Work (New York)

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Choice of velocipede was easier than I expected, for there was only one secondhand machine of my size, and when the handlebars had been changed (the old ones scraped the ground) I was left with a good bargain My early experience was salutary 14 years of motoring had involved different (if any) muscles and the saddle impinged on areas of my big-end which I had long forgotten Life on the roads as a glorified pedestrian seemed very different from the world of motorists, and it was most unnatural to have to stop at red lights But I persevered and rode daily to and from hospital As my reflexes, quadriceps, and some callosities developed appropriately, travelling suddenly became much more interesting Territory I had motored over a thousand times yielded unnoticed gems of architecture or nuances of gradient The prevailing wind started to play a part in my life I turned again to Nature and the basic things of life without which a man's spiritual development cannot take place—such as irritable little dogs, midges, and rain down the back of your neck Also you get a closer look at blondes in the bus queue Even securing the aid of a bicycle shop was a new experience, no garage has charged me as little as 2s for anything

Yes, cycling has reopened a dimension in my life Surprising what a few miles a day will do My weight is down, muscles are up, wind is longer, mind clearer, and waist more waisted It has been a wonderful week to recall, as I drive to my hospital with the heater on, listening to the radio

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faculty? Then indeed the " dissensions and bankruptcy " of which you warn us might well become a reality

Our seniors often tell us that there is no advantage to them from either course, and that they are only concerned to provide for the younger pathologists in whose hands the future lies At the same time they tend, perhaps, to ignore the experience of most of those who discuss such matters with these younger pathologists, and find that they are mostly in favour of a College The young men do not seem to be afraid of starting in a small way provided that they can feel genuinely independent and not a sort of appendage to another college Their " image " of pathology is of a subject which is of real importance in its own right and which can therefore expect its own separate and individual organisation

If we are to build surely for the future, independence is the only safe choice When I have reached retiring age, I do not want my juniors to be able to say to me " You and your colleagues made a fine mess of things in 1960 Here we are stuck in the College of Physicians where we are not really happy, but it will be very difficult to break away now If you had only made the effort to form a College it would be well established by now Did you *have* to choose the easy way? Couldn't you see just a little way in front of your noses?"

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Symposium

TICK-BORNE ENCEPHALITIS VIRUSES

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THE Institute of Virology of the Czechoslovak Academy of Sciences acted as hosts to virologists from eleven different countries during a four-day symposium last month on the biology of viruses of the tick-borne encephalitis complex The meetings were held in delightful surroundings at the House of Scientists at Smolenice, near Bratislava Representatives from almost all the major groups working on this subject were present, and the symposium provided an unusual opportunity for workers from many different disciplines to pool information and exchange ideas in a common approach In Britain, human infections with louping-ill virus do not present a serious public-health problem, but in Central Europe, Scandinavia, U S S R, and India viruses of the tick-borne encephalitis group are a serious menace The recent recognition of human infections with viruses of this group in Canada[1,2] and the U S A[3] extends the area in which these viruses are known

Dr J CASALS (New York) showed how the tick-borne viruses were placed with yellow fever and some twenty other arthropod-borne viruses into the serological group B on the basis of antigenic relationships In the past, the tick-borne encephalitis viruses have been considered a homogeneous group in spite of wide differences in the disease patterns they produced in different parts of the world Dr D H CLARKE (New York) showed that they could be divided into six antigenic subgroups on the basis of hæmagglutination inhibition tests with absorbed sera and by agar-gel precipitin tests The six subgroups were represented by the classical far-eastern Russian spring-summer encephalitis (R S S E), louping ill, Omsk hæmorrhagic fever, Kyasanur Forest disease,[4] Malayan tick-borne Langat virus, and Central European tick-borne encephalitis which included Czechoslovakian, Austrian, Finnish, Polish, Swedish, and Yugoslavian strains, as well as strains from European U S S R The recently described North American Powassan virus had not yet been examined by these techniques These antigenic differences were important because they explained the reported failure of R S S E vaccine to protect humans (Dr P N BHATT, Poona) or mice (Dr L DANEŠ, Prague) against infection with the virus of Kyasanur Forest disease

As in other branches of virology, tissue-culture techniques were gradually replacing older methods for the titration of viruses and for the detection of neutralising antibodies The use of a plaque technique for the titration of tick-borne encephalitis viruses was described by Dr J S PORTERFIELD (London) and was applied by Dr V MAYER, Dr J ZAVADÁ, and Dr R SKODA (Bratislava) to Central European strains Dr BHATT reported that chick fibroblast cultures were as satisfactory as mice for the primary isolation of Kyasanur Forest disease virus Czechoslovak workers preferred a two-stage process—primary isolation in tissue-culture cells which were later shown to be infected by virtue of their resistance to a challenge virus Neutralising antibodies were detected by a metabolic inhibition test carried out in Hela cells (Dr H LÍBIKOVÁ and Dr J VILČEK, Bratislava), by plaque inhibition (Dr J S PORTERFIELD, London), or by the direct inhibition of cytopathic effect in Hela cells (Dr E MOLNAR, Budapest) or in pig kidney cells (Dr D MÁLKOVÁ, Dr Z MARHOUL, Dr V FRAŇKOVÁ, and Dr V ČERNY, Prague)

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ATHEROSCLEROSIS among senior consultants is to be expected and, within reasonable limits, is perhaps right and proper. But when it strikes among your contemporaries—chaps you were at school with—complacency is shattered. So I bought a bicycle, for has it not been clearly shown by the work of whoever it was that exercise and coronaries were negatively correlated? Admittedly the idea was not entirely my own. Not long ago I chanced on a visiting physician of some eminence, washing himself down in the hospital cloakroom. He explained that he had just pedalled over from Fulham, a good fourteen miles away.

Choice of velocipede was easier than I expected, for there was only one secondhand machine of my size, and when the handlebars had been changed (the old ones scraped the ground) I was left with a good bargain. My early experience was salutary. 14 years of motoring had involved different (if any) muscles and the saddle impinged on areas of my big-end which I had long forgotten. Life on the roads as a glorified pedestrian seemed very different from the world of motorists, and it was most unnatural to have to stop at red lights. But I persevered and rode daily to and from hospital. As my reflexes, quadriceps, and some callosities developed appropriately, travelling suddenly became much more interesting. Territory I had motored over a thousand times yielded unnoticed gems of architecture or nuances of gradient. The prevailing wind started to play a part in my life. I turned again to Nature and the basic things of life without which a man's spiritual development cannot take place—such as irritable little dogs, midges, and rain down the back of your neck. Also you get a closer look at blondes in the bus queue. Even securing the aid of a bicycle shop was a new experience, no garage has charged me as little as 2s. for anything.

Yes, cycling has reopened a dimension in my life. Surprising what a few miles a day will do. My weight is down, muscles are up, wind is longer, mind clearer, and waist more waisted. It has been a wonderful week to recall, as I drive to my hospital with the heater on, listening to the radio.

* * *

The Comet journey to New York was a revelation in quietness, and in the extraordinary deep blue of the sky at 40,000 ft.

Lima to La Paz was more spectacular than I had imagined. After 500 miles of Peruvian desert, with the snowcapped Andes visible from 100 miles away, we went 200 miles east at 18,000 ft., just clearing the pass between the peaks. The main impression is the extraordinary colour. Over Peru it was an orange brown, with the river beds looking like skeletons of leaves pressed in grandmother's book. Then came a range of colours like those seen near the waste heaps of a chemical works, with greens and blues and greys and yellows. But since there is the largest deposit of minerals in the world here, perhaps it is no wonder. The magnitude of the scenery surpasses anything I saw in Tibet, though perhaps that's not quite fair since I've travelled more here. But in an hour or so we went by jeep past snow-covered llamas in the frosty morning, down a series of hair-pin bends dug out of a mountainside at 10° to the vertical at times, until we came to a deep valley with bananas and apples and oranges growing. Every half mile or so there are little crosses to mark a too enthusiastic driver, because there are no walls or edges to the road.

* * *

The practice of medicine in a foreign country is full of unexpected little quandaries and hazards. It's a commonplace that one's knowledge of anatomy dwindles rapidly from the day of passing the M.B., but it's not until you have to ask someone in a detailed way about their symptoms in a foreign language that you fully realise how many parts the body has. And different languages imply, so often, different points of view, for instance, we are taught in school that *s'asseoir* means *to sit down*, yet if your patient is lying flat and you want him to sit up you say *asseyez-vous*. Again, the French do not make quite the same distinction in their language as we do in ours between pain and grief, *douleur* means both. Somewhere since Malory wrote about the dolorous wounds of Arthur's knights, we have apparently forgotten that grief may be the real trouble underlying a patient's complaints of pain. Perhaps the trickiest problem one encounters in examining a patient abroad is that of vocal fremitus in the chest. Each of us solves this in his own way and one musn't be too rigid about it all. It would perhaps be a mistake to carry too far the customs of the Old Country into Basutoland where, I'm told, the word for 99 is Machoumearobilengmonoolemongametsoarobilengmonoolemong.

* * *

Reading the remarks of my colleague, lately of Lambeth, about the neighbours who persisted in addressing him as "Mister", I wondered whether he invariably refers to himself as "Doctor". Outside working hours I reserve it for certain well-defined occasions. One of these is when making appointments at the hairdressers. There by suggesting that I am terribly busy and liable to be called away at any moment, it facilitates excuses for missed appointments and enables me to get a quick shampoo and set at short notice. Again, I always use the title when I am asked to sign my name and address on the back of cheques, under these circumstances any extra evidence of respectability is of great help.

Lately it saved me from a good deal of inconvenience. My scooter was stolen from a part of London many miles from where I live. Late the same evening, the police rang to say that they had found it, and would I come to the station at once to collect it and sign the charge-sheet. Grateful but weary, I said that I would be there as soon as possible in view of the distance and the hour. "You wait there, Doctor, and we'll send a car," the station officer assured me, doubtless with the idea that at any moment I might be called upon to save a life, and the car duly arrived.

There are times, of course, when I deliberately avoid the title, but my landlady disapproves strongly of any attempts at dissimulation. If people ask for me on the phone as "Miss   " or use my Christian name, I hear her answer sternly, "I'll see if The Doctor is in."

* * *

Comparative textual criticism can be fun. Study of Baedeker's post-war (1958) guide to Austria and the 1929 edition provides a revealing gombarison—sorry, comparison. Though the familiar red cover with gold lettering is retained, it is no longer teutonically tubby but svelte. It contains 294 pages compared to 518, 100 of which were devoted to "Budapest, Prague and the north Bohemian spas", now omitted. (Though Hungary and Czechoslovakia had been independent countries for ten years, one would hardly gather it from the 1929 edition.) The present edition, now called an autoguide, is streamlined in other ways besides format: for instance, we no longer have blow-by-blow accounts of museums and picture-galleries with exhibits thought worthy of notice by Herr Karl mentioned in each room. There is less ancient history and esoteric information: thus we are no longer told that the Dragon Fountain or Lindwurmbrunnen in Klagenfurt is made of "chorite schist" but I was glad to see that the tablet commemorating Emanuel Hermann (1839–1902), "who invented the postcard", is still mentioned. Nor are there detailed tours of each town, starting from the railway station, but much clearer plans with "sight-seeing tours" and "through routes". In fact, modern travel is clearly no longer designed either to broaden the mind or flatten the feet. But nostalgia is catered for by the occasional survival of some of the classical phrases such as "Gasthof Lukashof, plain but well spoken of", still recalling one's aunt or members of the Women's Institute.

* * *

O, my Luve's like a red, red rose
I hope it's nothing catching.

Letters to the Editor

FUTURE ORGANISATION OF PATHOLOGISTS

SIR,—A voting paper is about to be circulated to pathologists asking them to record their opinion for or against a division of pathology within the Royal College of Physicians, or a new College of Pathology

We have for many years been concerned with research in pathology and with the training of pathologists, and believe that a higher examination based on a background of suitable training is essential to ensure that candidates either for hospital or academic appointments have acquired a reasonable grounding in their subject

We both write as past presidents of the Association of Clinical Pathologists, who have been openly critical of the procrastination of the Royal College, but who are satisfied that the suggestions now put forward by it are what is required Undoubtedly, the Royal College has been unduly tardy in making any suggestions, but the present generous and unequivocal terms make amends

It is generally agreed that in modern conditions the membership is an unsuitable examination for pathologists In the time available the techniques of clinical examination and of pathology cannot both be mastered

We welcome the opportunity of still closer cooperation with our clinical colleagues Not only are they progressively more dependent on us for confirmation of diagnosis, or indeed in many cases for provision of all the important data, but, reciprocally, we also are dependent on their acumen and powers of selection for our daily interests

We have long believed that what is needed is

(1) A higher qualification of the same status as the M R C P and F R C S

(2) An academic centre which would uphold the standards of pathology and help in maintaining good standards of training in pathologists

(3) A body to speak for pathologists

In our opinion the suggestion of the Royal College satisfies these requirements We believe that unless this opportunity is accepted there will be a very long delay before we realise our ambitions

JOAN TAYLOR
R J V PULVERTAFT

London

SIR,—Much has been said and written on this subject by the more learned and senior practitioners of our specialty, but little by the juniors As one of their number may I put forward three points

The primary reason for any alteration in the present position is to ensure recognition of the status of pathologists, despite the fact that a man's status depends above all upon his personality and the quality of his work, and only secondarily upon his qualifications Higher qualifications, however, are necessary to prove adequate training in one's own specialty for promotion to consultant or similar grade, and the institution of a specialist examination in pathology, of the highest standard, is now urgently required To the pathologist in training it is the most important facet of the present discussions The expenditure of time and work by those who aspire to the membership of one of the Royal Colleges of Physicians has been eloquently described by Professor Cappell in his presidential address [1] to the Association of Clinical Pathologists It is certain that only the qualification offered by the Royal College of Physicians will have the immediate high standing required to divert them from such examinations

The finances of the new organisation are of particular interest to impecunious registrars and lecturers It has been said that the provision and maintenance of any reasonable building will cost each member an initial donation of about £100 and an annual subscription of up to £25! Some of us may not be able to find such a sum Are we to be excluded from the college until we are senior enough to afford the subscription, and if so will we ever achieve the seniority? However, we are assured that industry and various benevolent foundations will provide the necessary funds Even if the money is forthcoming, I do not believe we can justify spending such vast sums on establishing a college, when there are so many research projects urgently needing finance Would our money not be better spent on research on acute leukæmia in children or even coronary disease in pathologists than upon a building? £100,000 would buy a lot of knowledge of disease—could we not devote our benefactions (if any) to establishing a series of research fellowships rather than a college?

If a College of Pathology is to be founded then I believe it must be as broadly based as possible and must be open freely to all those who work in and around the subject, scientist or doctor, whether academic or clinical Pathology is neither practised nor advanced solely by those on the Medical Register However, in a Faculty of the Royal College of Physicians it would be logical to restrict full membership to the medically qualified

The College of Physicians of London is a body of the highest standing and to be called a physician is no dishonour I hope, with Peter Davey,[2] that a Faculty will be established They offer us more than does an independent college in the foreseeable future, and at less cost The generosity of their terms puts us in an immensely strong position, and we can always withdraw

Finally, may I suggest abandonment of the term "Division of Pathology", for the words come uncomfortably close to the truth

London, S W 15 P O'GORMAN

*** Another view on this subject is given on p 1025 in a letter from the Widdicombe File —ED L

ATHEROSCLEROSIS AND CORONARY HEART-DISEASE

SIR,—Surely your correspondents are arguing on points of semantics rather than pathology As you, Sir, rightly pointed out last year,[3] patients do not suffer or die from coronary disease, but from the consequences of myocardial ischæmia, which may be acute, chronic, or spasmodic I have always held that one of the best classifications of disease causation, is that which we learned at our obstetrician's knee, of which a part ran—faults in the powers, faults in the passages, faults in the passenger Myocardial ischæmia may be due to faults in the power of the heart's action, faults in the coronary passages whether narrowed or occluded by what you will, or faults in the passenger—the blood, which may be deficient in oxygen-carrying capacity, or contain a substance noxious to the myocardium

In spite of the welter of investigations on atheroma and degenerative heart-disease, we remain remarkably ignorant as to the frequency, degree, and type of myocardial ischæmic change to be found at death in the population as a whole, and without this many of our deductions in this field are insecure I believe that a study, almost completed here by Dr C J Schwartz and Dr J R A Mitchell, will give us this information, as far as the current Oxford postmortem population is concerned, and may encourage others to carry out comparable investigations elsewhere

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[1] Lancet, Oct 15 1960, p 863

[2] See ibid Oct 22 1960, p 921

[3] Lancet 1959 ii, 863

No-one would dispute that one may find coronary narrowing or occlusion in hearts from persons of all ages, yet it remains that in a high proportion of elderly persons, ischæmic myocardial lesions occur, which are quite different in character from those usually seen in the younger age-groups, for example, there is the condition which Linzbach called reticular myocardial necrosis, but unhappily this is a sphere of cardiac pathology which to a large extent is unexplored

Turning to the Registrar-General's statistics, we find some curious features

England and Wales Crude Death rate to a million living

	1940	*1949*	*1958*
Arteriosclerotic heart-disease, including coronary disease (I S C. 420)	573	1093	1863
Myocardial degeneration with arteriosclerosis (I S C. 442 1)	467	617	532
Other myocardial degeneration (I.S C 422 2)	1548	1274	656
Total degenerative heart-disease (I.S C. 420 — 442 1 2	2588	2984	3051

As everyone knows, the death-rate attributed to " arteriosclerotic heart-disease and coronary disease " has increased more than threefold in the past eighteen years, but " myocardial degeneration with arteriosclerosis " has hardly changed at all and " other myocardial degeneration " has fallen to a third, so that if one groups together the rubrics that can be regarded as representing ischæmic heart-disease (I S C 420, 422 1, 422 2), the rate has only increased by a fifth, which is little more than is to be anticipated in view of the increased expectation of life I am, of course, as aware of the defects of comparison of crude death-rates as against standardised mortality ratios, as I am of the answer which John Graunt found to his question, why there were so few deaths attributed to the Pox in the Bills of Mortality Nevertheless, it might be worth while, for those who believe, that by feeding rabbits or men on unnatural diets, they will determine what factors in modern life have caused this spectacular increase in deaths attributed to " coronary disease ', to try and find out what are the factors which have caused the almost equally spectacular decrease in deaths attributed to " myocardial degeneration "

When we look at the age-differences, the Registrar-General's tables reveal another curious feature

England and Wales Age differences

	Proportion of Deaths Over 65			*No of Deaths 1958*		
	1940	*1949*	*1958*	*<65 yr*	*65 + yr*	*Total*
All causes	53%	63%	68%			
Arteriosclerotic heart-disease including coronary disease (I S C. 420)	55%	65%	69%	25 962	58,079	84,041
Myocardial degeneration (I.S C. 422)	85%	90%	95%	2195	51 577	53 772

As is to be expected in an ageing population, the proportion of all deaths occurring over 65 is steadily rising, in 1940 it was 53% and in 1958 68%, and the proportions of deaths attributed to arteriosclerotic heart and coronary disease is almost identical (1940 55%, 1958 69%), but of the deaths attributed to myocardial degeneration, 85% occurred at 65 and over, in 1940 and 95% in 1958

Putting this in another way, in 1958 there were 138,000 deaths attributed to " arteriosclerotic heart and coronary disease " and " myocardial degeneration ", of which only 20% occurred under the age of 65 Of these 28,000 deaths under 65, 94% were attributed to arteriosclerotic heart and coronary disease, whereas of the 110,000 deaths over 65, 47% were attributed to myocardial degeneration

There are clearly a number of explanations for this difference, but it must be assumed that certifying doctors consider that there is a fatal form of heart-disease which they designate as " myocardial degeneration " or any of the other inclusion terms in rubric 422, which occurs almost exclusively in persons of 65 and over, and accounts for nearly half of the cases of degenerative heart-disease in this higher age-group

Naturally we have no idea what, if any, are the clinical differences or morbid anatomical lesions in cases attributed to these two rubrics but if there are real differences, other than the whims of nomenclature of the certifying doctors, then it would be in keeping with Dr Acheson's[4] observations

Department of Pathology,
Radcliffe Infirmary,
Oxford

A H T Robb-Smith

SARCOIDOSIS TREATED WITH CHLOROQUINE

Sir,—I have read with interest Dr Soderstrom's article of Oct 29 in which he described the response of two patients with sarcoidosis to mepacrine He suggested that chloroquine may be used instead of mepacrine

I have treated with chloroquine systemic lupus erythematosus, periarteritis nodosa, Stevens-Johnson syndrome, and other hypersensitivity states since 1953 and rheumatoid arthritis since 1954 [5] [6]

The ætiology of sarcoidosis is still unproven, but there is a fairly strong suggestion that hypersensitivity may again play a part Michael [7] and Cummings,[8] for instance, related sarcoidosis to the chemical constituents of pine pollen

On the assumption that sarcoidosis represented a hypersensitivity state I have treated two cases with chloroquine since 1957

A married woman, aged 32, was first diagnosed as sarcoidosis, involving mainly the lungs, in 1956 when treatment was started with chloroquine sulphate 200 mg t d s This was continued for six months when it was stopped because of pregnancy By then all lung lesions had cleared Her condition was reviewed in 1957 and 1958, when she was quite well and the X-ray films showed clear lung fields

A married woman of 23 was first seen in July, 1957, when she had characteristic sarcoid lesions on her upper arms, trunk, and buttocks, and hilar-gland enlargement Biopsy confirmed the clinical diagnosis The Mantoux test was negative Chloroquine sulphate 200 mg t d s was started in July, 1957 In September, 1957, the hilar enlargement had greatly diminished and the skin lesions subsided In February, 1959, she was entirely symptomless and stopped chloroquine on her own By May, 1959, there was a recurrence of lesions on the right side of her cheek, upper arms, and buttock Chloroquine was immediately re-started, and by July, 1960, the skin lesions had almost completely disappeared and she felt well This patient is still on 200 mg chloroquine sulphate daily

At the international conference on sarcoidosis in Washington, D C , this year several speakers described the beneficial effect of chloroquine in sarcoidosis

Evaluation of any drug for sarcoidosis is difficult because of the fluctuation in the natural history of the disease with frequent spontaneous remissions This was the reason for not publishing my own limited experience of the drug in sarcoidosis If, however, since it appears that more widespread trials of chloroquine in the management of sarcoidosis are carried out in other parts of the world, then even a very limited trial such as Dr Soderstrom's and my own should be made known It is of particular interest that Dr Soderstrom noted selective staining of sarcoid lesions by the antimalarial There is reason to believe that chloroquine, too, has a selective action on the joints in rheumatoid arthritis, as we have found after 18 months' experience with chloroquine injections into rheumatoid arthritic joints (details are about to be published)

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[4] *ibid* 1960 ii 706
[5] Fuld H *Rheumatism*, 1958 14, 12
[6] Fuld H Horwich L *Brit med J* 1958 ii 1199
[7] Michael M Jr *Ann intern Med* 1956 45 151
[8] Cummings M M Hudgins, P C *Amer J med Sci* 1958, 236 311

Sefton General Hospital,
Liverpool H Fuld

HEATSTROKE

Sir,—I must congratulate you on your editorial of Oct 15 Such is the reputation of your journal, however, that unless I take issue with you on a matter of emphasis it may appear that treatment in a special room with refrigerated water, as described by Guthrie and McCraken,[1] is the best and only satisfactory method of treatment I know that special rooms of this nature are provided in the Persian Gulf—but many a heatstroke has been treated successfully with only the minimum of facilities I feel that it would be better to emphasise the principles of treatment rather than the accessories, which are expensive

At the moment there appear to be two schools of thought on treatment one uses refrigerated water or iced baths or iced sheets and the other artificial sweat and forced air movement I am a convert to the second school ever since I encountered shivering as a response to treatment with iced sheets in a patient who was still hyperpyrexial After this I began to reconsider the physics of reducing body temperature

Everyone knows that during treatment it is important not to reduce the temperature to normal limits as this may give rise to shock, and if shock occurs it is very difficult to treat Immersion in an iced bath can be very "shocking" to even a normal individual just jump naked into the Serpentine next January if you wish to contest this point! Immersion in, or spraying with, refrigerated water coils the body by conduction alone and is associated, sooner or later as the body cools, with peripheral vasoconstriction This vasoconstriction converts the skin, with its superficial fat, into a fairly useful insulating layer

Heatstroke is related to cessation of sweating however caused Evaporation of sweat from the skin, by virtue of the latent heat necessary to effect this, rapidly cools the blood flowing through the dilated skin vessels, which then act as a heat exchanger to the internal organs When sweating has ceased it is logical to provide artificial sweat in the form of tepid water and to aid evaporation with strong air movement In hot climates a powerful fan and tepid water are almost universally available, and it is usually possible soon to accelerate cerebral cooling with an ice bag, or even ice wrapped in a towel, applied to the head

I have no wish to decry the work of anyone who uses refrigerated water or iced baths, because I feel that in their experienced hands this form of treatment is both successful and safe To the average doctor, however, heatstroke is a comparatively uncommon emergency and treatment must be given at once with facilities readily available I can assure you that it is perfectly possible to treat successfully hyperpyrexia of any ætiology by sponging with tepid water and a strong air blast from a fan, even in conditions of high relative humidity and high ambient temperature

R.A F Institute of Pathology and
Tropical Medicine,
Halton Aylesbury Bucks R Mortimer

Sir,—Your leader is very valuable Hyperthermia (as we used to call it) will follow the treatment of patients with malaria, sandfly fever, enteric fever, and influenza in uncooled hospital wards Cardiac failure is uncommon in hyperthermia, except when the condition has persisted untreated for some hours

Servicemen have been known to report sick, with pyrexia, and been sent back to their quarters, and found hyperthermic and unconscious some hours later, in such cases cardiac failure is not uncommon and the response to the most enlightened treatment is disappointing

As you say, proper application of the principles of prevention, which are well known, should be everywhere applied, especially in Service communities, and devices for effective cooling should be at hand in all situations where heatstroke is known to occur I emphasised this in 1937 [1]

St Margaret's Hospital,
Epping Frank Marsh

SPONTANEOUS FRACTURE OF THE FIBULA

Sir,—Dr Hobbs (Oct 22) raises an interesting point when he states that in fatigue fractures of the fibula no adequate explanation of their occurrence has been given

These fractures occur in two main groups (1) the young and athletic and (2) the middle-aged and tired The case described clearly is of the second type Fatigue in bone may be compared in some respects to that in other materials such as metal When a metal column is subjected to repeated eccentric loadings, alternating tensile and compressive strains occur and eventually lead to a fatigue or stress fracture This also happens experimentally in bone Gaynor Evans [2] reported on subjecting a piece of fibula to repeated cyclical loadings at 5000 lb per square inch, and after 3,000,000 such loadings fatigue fractures occurred

In life, however, bone has a built-in capacity to repair by osteoblastic action and only when the stimuli are repeated sufficiently within the time taken to repair is a fatigue fracture liable to occur This period is likely to be prolonged in the middle-aged Even then, if aching causes the activity to cease, the early fracture may pass unrecognised

Windsor Roy Maudsley

POLIOVIRUS-NEUTRALISING ANTIBODIES IN STOOLS

Sir,—Dr Godtfredsen's letter of Aug 13 reported failure to demonstrate poliovirus-neutralising antibody in the stools of 13 convalescent individuals We appreciate being informed of these results and hope that she and others will not cease efforts to determine the nature of resistance of the human alimentary tract to poliovirus following infection with wild polioviruses or the feeding of attenuated living poliovirus vaccines Such alimentary resistance does not accompany Salk vaccination

Our communication [3] reported the demonstration of specific antibody in the stools of 13 children recovering from poliomyelitis Actually this represented only the positive results, the tests were performed in 93 convalescing patients and *only* 13 individuals were positive Once a given stool is demonstrated to contain type-specific poliovirus antibody, the observation can be repeated and appreciable loss of titre through storage and re-thawing has not been observed The serotype of antibody observed in our 13 positive children were 5 for type 1, 3 for type 2, 4 for type 3 One child's specimens neutralised types 1 and 2 When antibody was found in the stools the same type (and of course one or both remaining types) of antibody was found in the serum As we pointed out, the stool antibody when found was always *heterotypic* to the infecting virus, suggesting that those individuals' alimentary tracts had had previous exposure(s) to poliovirus

Deviations in Dr Godtfredsen's technique from ours include our use of a suspended-cell technique, which has advantages in demonstrating "low-avidity" antibody, and our use of 0 25 ml of the stools tested instead of 0 1 ml

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[1] Guthrie J, McCraken, A V *Lancet*, 1960, i, 682

[1] British Encyclopædia of Medical Practice vol vi, p 396 London 1937

[2] Gaynor Evans, F Stress and Strain in Bone Springfield, Ill, 1957

[3] *Lancet* 1959, ii, 272

Whether the test details per se are important is uncertain, but more children may need testing our record of 13 of 93 individuals (± 14%) suggests this Failure to demonstrate in vitro neutralising antibody of the usual kind in the stools of the remaining 80 patients may be purely technical or may have fundamental explanations The age of patient, time of stool-collections after the current infection, previous alimentary contact with the other serotypes of poliovirus, the "secretor" status of the patient's alimentary tract, and other factors may influence the results

Ascertaining the modus by which the alimentary tract resists infection after experience with live virus but not following intramuscular vaccination is important from the epidemiological, clinical, and general biological points of view It is hoped that studies of this kind with varying approaches in technique will be conducted by as many workers as can interest themselves in this field

University of Louisville, Kentucky

ALEX J STEIGMAN
MURRAY M LIPTON

STERILISATION OF THE DIABETIC'S SYRINGE

SIR,—The recent correspondence on this subject recommends several methods to be safe and trouble-free

On the one hand, Dr Wauchope (Sept 10) doubted whether sterilisation was necessary and described her fortunate personal experience without any infections for many years But I fear that many insulin patients would have less high standards of cleanliness than hers and this is a very important point not mentioned in the previous correspondence How well I remember a young woman who, after five years of trouble-free injections, developed mysterious abscesses on both thighs The bath she received on admission to hospital for investigation stopped all further troubles, and she told me that she had moved to a house where there was no bath and this explained her abscesses

What do the insulin manufacturers say in their insulin packages? Nothing very definite. Most of them say that boiling in tap-water is desirable but as that is not always possible, advocate keeping the syringe and needles in spirit

The balance of the advice given by your correspondents is to favour spirit alone, although the initiator of the correspondence, Dr Stephen Carter, boils his syringe four times a year and uses no spirit

London, W 1

R D LAWRENCE

SUICIDE

SIR,—Reading Dr Stewart's article of Oct 22 it is difficult not to feel compassion for many of the 85 suicides in his series of 122 who had been suffering from various painful or disabling diseases

Is it not time that the coroner's court formulæ, "while the balance of his mind was disturbed" or "while of unsound mind", should be discarded in the absence of clear evidence of mental disturbance prior to suicide? Some people who commit suicide to terminate a life that has become a life-sentence of intractable pain are taking a step that seems sensible albeit desperate

As you report last week (p 976), a Bill to provide that suicide and attempted suicide should no longer be criminal offences has been drawn up and approved by the Criminal Law Revision Committee So need we penalise the suicide by casting an unmerited slur on his sanity just because he has committed suicide?

With regard to attempted suicide, Prof E Stengel[1] has for a long time taught that one of its main motivations is the appeal of a desperate individual for help from his fellow-men Unless the family or friends of the attempted suicide are alerted to his dangerous dilemma by the suicidal attempt, the only practical step likely to prevent a second, possibly successful, attempt would seem to be bringing him before the courts and placing him on probation on condition that he receives necessary psychiatric treatment It is to be hoped that this potentially lifesaving course will not be made more difficult if the new Bill becomes law

London, W 1

F R C CASSON

THE NATURE OF ESSENTIAL HYPERTENSION

SIR,—I really must take exception to the data which Dr Marshall (Oct 22) alleges add to the solution of this problem, and the conclusions he draws from these data

My old chief, Sir Thomas Lewis, would not allow readings of blood-pressure taken by nurses to appear in scientific publications The estimations which Dr Marshall uses were made by "specially trained nurses at hourly intervals during one day a patient spent in hospital" They were made to the nearest even number Dr Marshall states that digit preference can be excluded because the nurses had no incentive Nor had those employed by Boe, Humerfelt, and Wedervang[1] in their measurements made on 67,976 inhabitants of Bergen Yet digit preference was more marked than in any other series I know 85% of systolic readings (series I) ended with 0 and only 15% with 5 For diastolic readings the percentages were 87 and 13 respectively Diastolic pressures had a bimodal distribution in the second but not in the first sample This bimodality was most probably due to a change in the team of nurses making the measurements There is no analysis in Dr Marshall's paper of the distribution of readings, nor any evidence that steps were taken to assess how accurate the readings were

As disturbing is his statement "Moreover, the blood-pressure figures used in this study were means of six readings taken under constant conditions" To those who work in the field of science, "constant conditions" has a clear implication, and is a state, in fact, very rarely achieved Dr Marshall's 134 patients "attended hospital for one day during which they rested on a bed in the supine position Their blood-pressure was recorded hourly for six hours by specially trained nurses, who read the sphygmomanometer to the nearest even number" One could perhaps imagine that from 10 to 4 the patients lay on a bed in a side-ward and were visited only by the nurses But this was not so "During the one day in hospital the patients had a physical examination, chemical and microscopic examinations of the urine, estimation of the blood-urea and blood-cholesterol, an electrocardiogram, and a radiographic examination of the heart and skull"

Dr Marshall's averages of six values, each to the nearest even number, will give him a series of integers which perhaps he might take to one place of decimals As set out they are arranged in groups at intervals of 8 or 12 mm Hg He does not say how this grouping has been done And yet it is vital to the conclusion the reader is invited to accept

However, the worst feature of Dr Marshall's paper is his evidence for bimodality A protest has been made before against interpreting irregularities in frequency distribution curves as bimodality, especially when the numbers are small Fortunately Dr Marshall has now brought this practice to what must be the all-time low

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[1] *Lancet* 1952, i, 1059

[1] Boe J, Humerfelt S, Wedervang, F *Acta med scand* 1957 suppl 321

He says " The systolic pressures of patients over 60 years had a bimodal distribution irrespective of whether their parents died below or above the age of 65 (fig 5)" Fig 5 shows the frequency distribution curve of 26 patients whose parents had died under the age of 65 Here are data taken from fig 5 for this group

Systolic B P	*Frequency %*	*Actual number*
108	4	1
120	12	3
132	4	1
144	8	2
156	12	3
168	24	6
180	16	4
192	8	2
204	12	3
Total	100	25

The contention evidently is that a series 1 3 1 2 3 demonstrates bimodality

Finally, supposing that an analysis of patients between the ages of 31 and 70 showed that there were essentially two populations as regards blood-pressure—and has this not been shown by Dr Marshall ?—could this be accepted as evidence that essential hypertension is the manifestation of a single gene ? For Dr Marshall states " It seems likely that the appearance of a group with raised blood-pressure is caused by a hereditary factor—probably, as Platt suggested, due to a mendelian dominant " It should be clearly stated that cerebral vascular disease consists of at least three entities occlusion of the arteries in the neck, of those within the cranium, and cerebral hæmorrhage There is a strong suspicion that the last is more closely associated with grossly raised pressure than the first of these Dr Marshall says that these patients had " what was judged on clinical grounds to have been a non-embolic cerebral infarction ", but, as previously reported,[2] his trial of anticoagulant treatment had to be stopped because of the incidence of fatal cerebrovascular accidents due to cerebral hæmorrhage in the treated group Had he indeed demonstrated two populations in cases of cerebrovascular disease this would have no bearing whatsoever on whether essential hypertension is or is not the manifestation of a single gene

Oxford G W PICKERING

SIR,—Before some of your readers should be tempted to interpret the results found by Dr Marshall as cogent evidence in the conflict of views on the nature of essential hypertension, could we have the answers to some simple questions ?

(1) We are told that the subjects studied had all previously had what was judged to have been a non-embolic cerebral infarction In what ways were these survivors thought to be representative of all people suffering cerebral infarction, how were the subjects selected, and why were there 91 males and only 43 females when mortality-rates from vascular lesions involving the central nervous system show no gross sex difference

(2) Having demonstrated such very different frequency distributions of arterial pressure in the two sexes as those shown in fig 1 (*b*) and (*c*), what is the justification for combining the two sexes in all subsequent analyses ?

(3) In analysing blood-pressure data for subjects aged 31-70 is it reasonable to use only two age-groups, above and below 60, when the evidence derived from the general population shows arterial pressure to be very sensitive to age ?

(4) The grouping of pressure into units of 12 mm Hg for systolic and 8 mm for diastolic pressure is unusual Could this have influenced the shape of the published curves ?

The type of study carried out by Dr Marshall could be repeated in many hospitals in the country but have little value unless confirmed in less highly s populations Before we are confused by more an bimodal curves, may I make a plea, Sir, that should publish their data in a form that enables int readers to evaluate them and allows comparison wit published work, and particularly with the careful Platt and Pickering Pictures alone are unsatisfac

Llandough Hospital,
Penarth, Glamorgan W E Mi

SIR,—There seems to be a growing and unfo tendency, especially in communications on hypert to argue from diagrams The latest example is th of Dr Marshall, who relies upon them entirely an no figures at all It must be admitted, however, t sin is a minor one, for as his numbers are very sm corresponding frequencies can be reconstructe almost complete accuracy from his curves shown centages Nevertheless, one would like to have th data in less coarsely grouped form And, incide how can pressures measured to the nearest even n be added so as to yield the series of figures sh group centres in all the diagrams ?

The following opening paragraph has appea chapter II in all successive editions of R A F *Statistical Methods for Research Workers*, right back first edition of thirty-five years ago

> " The preliminary examination of most data is facilitated use of diagrams Diagrams prove nothing, but bring outs features readily to the eye, they are therefore no substitute critical tests as may be applied to the data, but are val suggesting such tests, and in explaining the conclusions upon them "

The current discussion on the nature of es hypertension will be greatly helped if these wise wo remembered, and if authors give as much of thei data as possible, apply suitable tests, and in par explain just what they have done, desiderata str lacking in some recent papers The curves can the their proper purpose of illustration and light relief

M R C Clinical Genetics Research Unit,
London, W C 1 J A FRASER ROBE

SIR,—It has been pointed out to us that we wrong (Oct 15) in saying of Miall and Oldham's that there were only 24 subjects with diastolic pr " greater than 100 mm Hg " This should hav " 105 mm Hg and greater ", &c We are very so

S L MORRI
J N MORRIS
London, E 1

CYCLICAL ŒDEMA AND SHOCK

SIR,—I read with great interest your leading art Oct 1 You mentioned that apparently the urine w tested for hydroxyindole-acetic acid in the patie described [2]

In the interest of completeness, I should like to ad although we did not include this in the published r the 24-hour urinary excretion of 5-hydroxyindole acid was measured on 5 occasions in this patient, inc during a shock phase, during a recovery phase, and a time when she was asymptomatic These determin were performed by Dr O Dhodanand Kowles New York Hospital The values were all between 3 mg per 24 hours (normal up to 8 mg per 24 hou

New York. BAYARD CLARKS

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[2] Marshall J Pathogenesis and Treatment of Occlusive Arterial Disease p 99 London, 1960

[1] *Clin Sci* 1958, 17 409
[2] *Amer J med* 1960, 29 193

MODERN CLINICAL BIOCHEMISTRY

R,—I would not put the clock back 50 years as Dr dry forbids (Oct 29), but 113 years and quote from how's paper, Standpoints in Scientific Medicine can learn much from chemistry, but we will have to ve for ourselves the privilege of applying its findings " how was familiar with the appreciable number who Dr Hendry's outlook in his 1855 paper on Cellular ology he writes " The condescension with which the onents of chemical and physical viewpoints—even who have only a very imperfect understanding of oscopic anatomy—look down on morphology is known "

om my student days I have had the highest regard for d we receive from competent biochemists if they their right place in the team they are invaluable I ngly dislike splitting the pathology department into or more watertight compartments Whenever I look n my microscope problems in bacteriology, hæmato- , or biochemistry arise, with the aid of one or other mber of my team these are followed to the advantage of clinician and patient Our biochemist regularly draws attention to problems which should be followed in er departments Without a medical training very few chemists are safe in advising on the meaning of many their findings A good example of the interdependence the four departments of the pathological laboratory was man of 23 admitted to one of our surgical wards in a ate of diabetic coma When the biochemist told me of s very high blood-sugar I at once asked why he was in a urgical ward it was because he had had a bladder-neck peration for enuresis there three months before I discovered that he was not then a diabetic, so we at once amined his blood for severity of infection (if any), and is urine for pus and organisms The real diagnosis was uickly established as pyonephrosis, and unfortunately roved at necropsy To me all sections of the laboratory e equally important in general Who is the most important departmental head varies with the case, for the young an just mentioned I would say it was the hæmatologist ecause he said clearly death from infection is inevitable the absence of successful treatment

The question of who is the most important, the pathogist or one or other of the technical heads of departments, an absurd one It is well answered by Leo Tolstoy in s short story Three Questions written in 1903 (in *wenty-Three Tales*) I hope Dr Hendry and others who ink like him will read this The practical point is that pathologist is usually the only one who can bring all ctions of the laboratory to the aid of the clinician, he ove all others can cheat death when he calls too soon e greatest emotional satisfaction is to be found in neral practice, the greatest intellectual satisfaction in the ological department The former is warm, the latter o often cold, that is why many of us feel like Dr Hendry t times If this emotional satisfaction is wanted, do not ecome a physician or surgeon as Professor Cappell ossibly suggests, for they occupy a half-way position, btain a medical qualification and enter general practice

r Hendry may be shocked to know that to me the iochemist ranks equally with the senior technician in harge of hæmatology, bacteriology, and histology I do ot know which is the most important until I know the blem If the training of a biochemist is more difficult, d all will not agree with this, they should be paid re—as they are This makes a psychological barrier een them and the technical heads of the other departments which a wise biochemist will do all in his power to destroy

Biochemists are not at the crossroads looking four ways at once at the moment they are looking on the way out only If that happens it will be a tragedy We do not have far to look to see non-medical biochemists who are invaluable in the practice of medicine, they are professors or of that calibre This is taken to mean, by some, that all we need to do to obtain a good biochemical service is to appoint a good chemist in charge of it and then keep away This is nonsense My biochemistry department owes a lot to men with medical qualifications, these are ideal but in short supply Even Dr Hendry might allow that the greatest clinical biochemist of all time was the medically qualified Paul Ehrlich

How should the pathological services of the future be planned? Division into a number of watertight compartments is an evil which may be necessary in places The right thing seems to me a large general clinical laboratory where a problem in a patient is studied, not just a test performed This should be backed by small reference laboratories in the same building Most of the routine biochemistry should be done in the clinical laboratory—including the blood sugars and ureas for which Dr Hendry has such contempt, though if I could have only two biochemical investigations I would pick these

How should junior and senior members of the medical profession use the pathological services? I give two answers to this Because so many tests are needed the pathologist can no longer attend to all Many are straightforward and the patient progresses well, these cases justify a request for a given test Many patients are diagnostic problems or are unsatisfactory If a patient is, say, unsatisfactory after an abdominal operation I like the surgeon to tell me what he did and invite our help At the moment many are obsessed with biochemistry to the exclusion of the other branches The correct use of all departments will invariably say peritonitis, ileus, both or neither We want to know the process, not some minute detail of it When we begin our training with the microscope we use the highest magnification we can get, and feel that if we could only obtain something larger we would know everything As we become more experienced we use the lowest magnification so that we can see the process This earns us scorn from the most junior my son, when a dental student, assured me that I only guessed at such a low magnification I fancy that many, who should know better, feel that in biochemistry they have something of higher magnification than the electron microscope Perhaps they have, but the sap in a leaf tells you little about the plant and less about the forest.

May biochemists read Leo Tolstoy and remain our honoured colleagues May I be permitted to salute Professor Cappell's masterly survey

Derbyshire Royal Infirmary,
Derby

G R OSBORN

SIR,—There is an element of truth in Dr Hendry's statements about the interrelationship of " pathologist " and biochemists, but surely many will think he overstates his case, and confuses any serious analysis of the position, both by his caustic wit and blatant misuse of the names of the reactants It is patently absurd to imply that each large hospital should have an autonomous biochemistry department such a separist movement would be harmful to the patient and the clinician, and more particularly to

the biochemist himself What is clearly needed is a greater integration of the laboratory services, both within their own house and within the framework of the hospital as a whole No hospital worker, be he physician, surgeon, histologist, or biochemist, can go it alone, even if the latter thinks he can do it all himself It is, of course, platitudinous to say there is no place for the enthusiastic amateur in this modern scientific work, each specialist must overtly be trained as such, but he would be a fool indeed to suppose he alone has something to offer the patient, whatever the latter's disease

Pathology is the study of disease however Dr Hendry may interpret biochemistry to himself, in clinical practice it is the application of chemistry to the study of human disease, and it must follow that even he is to some extent a pathologist I personally would like the terms pathologist and pathology laboratory, as currently used, to be discontinued, in hospitals at least Instead, the terms bacteriologist, biochemist, biophysicist, hæmatologist, histologist, or virologist could be used according to taste each worker should have an individual laboratory, but all should be contiguous and in one central building, so having common meeting and stamping grounds Medicine and pathology have both suffered enough enthusiastic divisionists already without further chemical schizists

County Hospital,
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J R H Pinkerton

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Sir,—During the past three months I have been using short courses of intensive hydrocortisone 10 mg t i d for four days in severe cases of herpes zoster—with dramatic results

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Rugby

J A Wakis Miller

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Sir,—I read your leader of Oct 8 with much interest, because it fell to me to review this topic at the First International Conference on Congenital Malformations held in London in July, 1960

May I take this opportunity to encourage those readers who may be continuing to investigate the outcome of rubella in pregnancy to arrange for the assistance of a laboratory where virus diagnostic tests can be performed?

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Work done on the Echo viruses in Canada and many other parts of the world has convinced me that a diagnosis of "rubella" or "german measles" obtained from a patient must be considered unreliable Even a physician may mistake infection with an Echo virus (especially type 9) for rubella In differentiation, it is important to note the short incubation period of Echo infections (3–5 days)

Epidemiological studies such as those commented on in your editorial have produced substantial results Such studies may, however, prove even more rewarding in th future when epidemiological techniques are correl with the more precise laboratory techniques of th modern medical virologist

School of Hygiene,
University of Toronto

A J Rhodes

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Sir,—I have encountered this phenomenon of respira tory obstruction due to faulty endotracheal tube on three occasions Simple deflation of the cuff has relieved th obstruction immediately, and the operation has been proceeded with There is no need to change the tube

A few weeks after my first case our registrar encountered this mishap, and deflation of the cuff again reversed a potentially serious position

Morriston Hospital,
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J M Lewis

HAZARDS OF BARIUM-SULPHATE ENEMA

Sir,—Your annotation of Oct 8 refers to barium sulphate pulmonary embolism The following case may therefore be of interest as a record of a further hazard in relation to this common diagnostic procedure

A fit man of 70 was referred from the outpatient department for barium enema He complained of mucous diarrhœa Technically the enema was uneventful On walking from the X-ray table he complained of sudden severe abdominal pain and collapsed to the floor The radiologist reported that he was unconscious for some seconds He was transferred immediately to a general medical ward

When examined he was conscious, complaining of generalised abdominal pain and mentioned a transient sharp left-sided chest pain No peripheral pulses were detectable, blood pressure was unrecordable and the jugular venous pressure was raised It was then observed that a striking generalised erythema was developing it reached a maximum some 45 minutes after completion of the enema, and faded gradually over the next 6 hours

Immediate resuscitation was symptomatic, using oxygen, *morphine, intravenous pressor agents, and intramuscular* promethazine Chest X-ray, plain X-ray of the abdomen, electrocardiogram, serum-transaminases, and urinary 5-hydroxyindole-acetic acid were all subsequently shown to be normal The barium enema showed a few diverticula in the sigmoid colon but no other abnormality The patient made an uneventful recovery and was discharged 10 days later The cause of his abdominal pain remains obscure

In view of the negative findings and the clinical picture, this man may have had an acute hypersensitivity reaction The barium enema was made up in 1% tannic acid and was preceded by colonic irrigation with tap-water followed by 'Veripaque' enema A similar investigation 4 months previously with the same preparation was entirely uneventful Skin tests using 1% tannic acid were negative

Fatal collapse due to proven barium-sulphate pulmonary embolism has now been reported [1] A second case in which this diagnosis seems highly probable, although necropsy was not allowed, has recently been recorded [2] Acute "water intoxication" in the preparation of children for barium enema is now a well-recognised and sometimes fatal hazard [3–5] But the condition I have described does not seem to have been recorded previously

Over 1000 barium enemas are performed annually in this hospital, no member of the staff of the department of radiology has seen or heard of a similar case Although,

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I should like to thank Dr G D Hadley for his advice and permission to publish this case

Middlesex Hospital,
London, W 1

B R WEBSTER

ACUTE COPPER POISONING

SIR,—The paper by Professor Semple and his colleagues (Sept 24) is very timely, especially because the possibility of toxic hazards from copper heating vessels does not seem to be generally appreciated [1]

It may be of interest to recall that Dr Harold Jacobziner, assistant commissioner of the New York City Department of Health, commented last year on the toxic hazards of copper as well as other metals in hot tap-water drawn from corroded pipes lined by these metals [2] He said that he had in his files " the report of an investigation of a case where several persons became ill due to excessive copper in water drawn from the bottom of a hot water tank " Jacobziner was commenting on a paper [3] which had recommended the use of hot tap-water in the preparation of infant feeds

Memorial Hospital of Long Beach,
Long Beach, California

GEORGE X TRIMBLE

ORAL TREATMENT OF PERNICIOUS ANÆMIA WITH LOW DOSES OF H P P /1

SIR,—Dr Varadi (Oct 15) must realise how increasingly difficult it has now become for us to assess the significance of his findings, faced as we are with three differing descriptions of the treatment given, and the responses obtained, from the same ten cases It is also a matter of some surprise to find that he classifies a case as " relapsed " (Sept 17) when, in fact, the patient did not suffer a deterioration in the blood-picture at all, but merely a fall in the serum-B_{12} level when the daily dose was reduced from 300 µg to 100 µg of B_{12}

Finally, it is a little disappointing that Dr Varadi has still declined to explain the scientific basis of his interpretation of serum-B_{12} levels, when applied to this particular form of therapy We do not doubt that the estimation may be of some value in confirming a diagnosis in the untreated case of pernicious anæmia, but we would like to know what evidence he has for the conclusion in the penultimate paragraph of his letter of Sept 17, that serum-B_{12} levels also reflect the degree of intestinal absorption, *on this particular form of therapy*

St Helens Hospital

F S MOONEY
J G HEATHCOTE

SIR,—Like Dr Varadi and Mr Elwis (Sept 17) I have been investigating the serum-vitamin-B_{12} levels of patients with pernicious anæmia in relapse who have been treated with vitamin-B_{12}/peptide (' Distivit ')

In 8 such patients receiving 200 µg daily or less, followed for periods of three to eighteen months, the serum-B_{12} concentration rose above 200 µµg per ml in 1 case only A further 2 patients given 500 µg daily for a period of eighteen months maintained serum levels around 400 µµg per ml These results are broadly similar to those previously reported [4] using oral crystalline vitamin B_{12} With the exception of 1 patient receiving 100 µg daily, all these cases reached and maintained normal values of hæmoglobin, red-cell counts, and packed-cell volumes, so Dr Mooney and Dr Heathcote (Oct 1) could again, on this evidence alone, question the scientific basis for using serum-vitamin-B_{12} levels as proof of adequate dosage I submit however that, as a general concept of rational therapy, it is desirable to give a sufficient amount of the vitamin to maintain the serum level near the average normal mean—that is, about 400 µµg per ml It therefore seems necessary, if oral treatment for pernicious anæmia is considered desirable for a particular patient, that over 200 µg daily should be administered, whether the vitamin B_{12} is in a crystalline form or a peptide complex

Coventry and Warwickshire Hospital,
Coventry

N K SHINTON

BROADER MEDICAL TEACHING

SIR,—May I comment on your interesting annotation Broader Medical Teaching (Oct 22) ?

On Oct 23, 500 general practitioners attended our third *Medical World* Conference One of the subjects was " Training for General Practice " From the discussion, several attitudes became apparent

(*a*) The G P s agreed unanimously that their medical-school training had not fitted them for their work, (*b*) that, with few exceptions, hospital doctors who had trained them had little knowledge or understanding of the problems facing the G P , (*c*) that, despite a growing awareness of these deficiencies in training, the situation has not improved of recent years

In a laudable attempt to correct an unbalanced system of training, some universities and the College of General Practitioners have introduced schemes to allow medical students to see something of general practice during their training Apart from local schemes which allow students to spend a few weeks with selected G P s, there are the Edinburgh and Manchester University schemes On a more ambitious scale the Inverness Regional Hospital Board is providing rotating internships, which include attachment to G P s, and the Wessex scheme financed by one of the Nuffield Trusts is seeking to provide young G P s with a chance to see something of all three branches of the Service

No-one would wish to minimise these efforts Yet surely they leave the main problem unsolved The hospital teacher who will continue to form the minds of new generations of students is still out of touch with the problem of general practice How can this be otherwise when the career structure in the hospital field demands that the young trainee consultant should unremittingly follow the narrow lines of his specialty ?

I suggested at our conference that the problem could be partly solved if every future teacher in the hospital service had to spend a period in general practice—a proposal which was warmly welcomed The time to do so would be between the registrar and senior-registrar appointments—i e , before the young specialist sets his foot on the ladder from which he dare not fall off If the time spent in general practice were made a condition of appointment to a senior-registrar post, no-one would gain an unfair advantage

Unlike the G P trainees, these young aspiring specialists would not have to be taught general practice by selected good G P s Their need is to see the realities of practice in all its forms They could be attached to four different types of practice for six weeks each, and could learn quickly some of the problems facing the industrial, semi-urban, rural, and seaside G P In all, this would occupy only six months of their working lives, yet it could have a profound and beneficial effect on the future training of the medical student—and, indeed, on British medicine

London, W C 1

BRUCE CARDEW
Editor, *Medical World*

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1 *J Amer med Ass* 1960, 174 550
2 Jacobziner H *J Pediat* 1959 55 797
3 Fischer C Whitman, M *ibid* p 116
4 Marshall Chalmers, J N , Shinton, N K *Lancet* 1958, ii 1298

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J G HEATHCOTE

SIR,—Like Dr Varadi and Mr Elwis (Sept. 17) I have been investigating the serum-vitamin-B_{12} levels of patients with pernicious anæmia in relapse who have been treated with vitamin-B_{12}/peptide ('Distivit')

In 8 such patients receiving 200 μg daily or less, followed for periods of three to eighteen months, the serum-B_{12} concentration rose above 200 μμg per ml in 1 case only A further 2 patients given 500 μg daily for a period of eighteen months maintained serum levels around 400 μμg per ml These results are broadly similar to those previously reported [4] using oral crystalline vitamin B_1 With the exception of 1 patient receiving 100 μg daily, all these cases reached and maintained normal values of hæmoglobin, red-cell counts and packed-cell volumes, so Dr Mooney and Dr Heathcote (Oct 1) could again, on this evidence alone, question the scientific basis for using serum-vitamin-$B_{1\_}$ levels as proof of adequate dosage I submit however that as a general concept of rational therapy, it is desirable to give a sufficient amount of the vitamin to maintain the serum level near the average normal mean—that is, about 400 μμg per ml It therefore seems necessary, if oral treatment for pernicious anæmia is considered desirable for a particular patient, that over 200 μg daily should be administered, whether the vitamin B_{1}. is in a crystalline form or a peptide complex

Coventry and Warwickshire Hospital,
Coventry

N K SHINTON

BROADER MEDICAL TEACHING

SIR,—May I comment on your interesting annotation Broader Medical Teaching (Oct 22)?

On Oct 23, 500 general practitioners attended our third *Medical World* Conference One of the subjects was ' Training for General Practice" From the discussion several attitudes became apparent

(*a*) The G P s agreed unanimously that their medical-school training had not fitted them for their work, (*c*) that, with few exceptions hospital doctors who had trained them had little knowledge or understanding of the problems facing the G P , (*c*) that, despite a growing awareness of these deficiencies in training, the situation has not improved of recent years

In a laudable attempt to correct an unbalanced system of training, some universities and the College of General Practitioners have introduced schemes to allow medical students to see something of general practice during their training Apart from local schemes which allow students to spend a few weeks with selected G P s, there are the Edinburgh and Manchester University schemes On a more ambitious scale the Inverness Regional Hospital Board is providing rotating internships, which include attachment to G P s, and the Wessex scheme financed by one of the Nuffield Trusts is seeking to provide young G P s with a chance to see something of all three branches of the Service.

No-one would wish to minimise these efforts Yet surely they leave the main problem unsolved The hospital teacher who will continue to form the minds of new generations of students is still out of touch with the problem of general practice How can this be otherwise when the career structure in the hospital field demands that the young trainee consultant should unremittingly follow the narrow lines of his specialty?

I suggested at our conference that the problem could be partly solved if every future teacher in the hospital service had to spend a period in general practice—a proposal which was warmly welcomed The time to do so would be between the registrar and senior-registrar appointments—i e , before the young specialist sets his foot on the ladder from which he dare not fall off If the time spent in general practice were made a condition of appointment to a senior-registrar post, no-one would gain an unfair advantage

Unlike the G P trainees, these young aspiring specialists would not have to be taught general practice by selected good G.P s Their need is to see the realities of practice in all its forms They could be attached to four different types of practice for six weeks each, and could learn quickly some of the problems facing the industrial, semi-urban, rural, and seaside G P In all, this would occupy only six months of their working lives, yet it could have a profound and beneficial effect on the future training of the medical student—and indeed, on British medicine

London W C 1

BRUCE CARDEW
Editor, *Medical World*

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[1] *J Amer med Ass* 1960 174 550
[2] Jacobziner H. *J Pediat* 1959 55 797
[3] Fischer C, Whitman M *ibid* p 116
[4] Marshall Chalmers J N, Shinton, N K. *Lancet*, 1958 ii, 1298

Obituary

ALAN BROWN

M D Toronto, F R C P (C), F R C P

Dr Alan Brown was one of the pioneers of pædiatrics in Canada For over thirty years he was physician-in-chief to the Hospital for Sick Children in Toronto, and when a chair of pædiatrics was set up in the University of Toronto in 1935 he was appointed the first professor He died on Sept 7 at the age of 73

He qualified from the University of Toronto in 1909, and spent five years as a resident physician in the Babies' Hospital (Columbia University), New York After further postgraduate study in Germany, Austria, Denmark, and Britain, he was appointed to the medical staff of the Hospital for Sick Children in Toronto in 1915 Four years later he became its physician-in-chief Under his direction the hospital became a centre for the training of medical undergraduates, pædiatricians, and nurses In 1919 he was appointed an associate professor of medicine in the university, and in 1935 head of the newly created department of pædiatrics He served for many years as consultant to the local, provincial, and national departments of health, as well as to three other Toronto hospitals and the former Infants' Home He was a founder and past president of the Canadian Pædiatric Society He retired from his hospital appointments and his chair in 1951

As a writer and a visitor he was well known on both sides of the Atlantic His book on *The Normal Child*, first published in 1926, is now in its fifth edition, and with Dr F F Tisdall he published a useful survey of *Common Procedures in the Practice of Pædiatrics* He gave many clinical lectures, and his colleagues in this country will recall his Ingleby lectures in 1948 on the scientific construction of the normal child's diet He was a corresponding member of the British Pædiatric Society and was elected F R C P in 1940

E C R writes

"Alan Brown crusaded vigorously for many improvements in the care of infants and children, including the proper formulation and sterilisation of infant feedings, the compulsory pasteurisation of milk, and the universal use of diphtheria toxoid and other well-established immunisation procedures Soon after he became physician-in-chief, he organised a small research laboratory at the hospital which, with his support and encouragement, has grown greatly with the years in both size and reputation Canadian pædiatrics in general and the Hospital for Sick Children in particular owe a great deal to his vision, unusual energy, and outstanding organising ability "

Dr Brown married Miss Constance Hobbs in 1914 She survives him with their two daughters

CLAUDE WILFRED ALFRED KIMBELL

M B N Z , F R C O G , F R C S E

Mr Claude Kimbell, gynæcological surgeon to the Samaritan Hospital for Women, London, died on Oct 26 at the age of 55

A New Zealander by birth, he was educated at Wellington College and the University of Otago, where he graduated M B in 1930 The following year he came to this country for postgraduate studies, and in 1935 he took the F R C S E and in 1937 the M R C O G During the late war he served in the R.A M C with the rank of major He remained behind at Dunkirk to look after the wounded and spent the rest of the war as a prisoner in Germany Afterwards he returned to practise obstetrics and gynæcology in London and was appointed to the staff of the Samaritan Hospital and the City of London Maternity Hospital He was elected F R C O G in 1953 He was a founder member of the Gynæcological Travellers' Club

C M G , one of his colleagues at the Samaritan Hospital, writes

"Claude Kimbell was a sick man for many years, but because of his courage and interest in life he continued with his work In the Samaritan Hospital he was loved by everyone he worked with in the outpatient department, wards, and theatre. An excellent surgeon, he was interested in the total human and always concerned with the psychological implications of a case He was a perfectionist and ever ready to sacrifice himself for his patients and friends From his experience as a prisoner-of war he had learned not bitterness but a deep sympathy and understanding of his fellows "

J H , who first met Kimbell twenty-five years ago on visits to Liverpool when Kimbell stayed with his fellow New Zealander, the late Charles Marshall, came to admire "his many qualities as friend and surgeon" He relates

"Knowing that his health was failing Kimbell lately made a trip to Canada as a ship's surgeon to see his married daughter and grandchildren In a Newfoundland hospital he found a sailor who had been seriously injured four months previously No one would take the responsibility to send the sailor back to England and his family It was typical of Claude Kimbell that he organised a passage home on his own ship for this injured man, and on arrival in Liverpool with great energy arranged for him to be sent home to his family

"As a surgeon Kimbell was meticulous in detail and deft in technique As a man I can sum him up in four words—modest, honest, generous, and always considerate of others "

Public Health

The Registrar General's Commentary

In his commentary on the vital statistics for 1958 the Registrar General[1] notes that the birth-rate of 16 4 per 1000 was the highest recorded since 1949 There were 740,715 live births, the largest number since 1948 The birth-rate per 1000 women aged 15–44 was 82 1 in 1958, which was above the level of the early 1920s and 32% higher than the 1938 rate The birth-rate was highest in Merseyside and lowest in Greater London

Population —The annual rate of increase amounted to about 0 5% of the population, a little less than the average rate of population increase for Northern and Western Europe, and only a third of the rate of increase in Asia The estimated total population at mid-1958 was 45,244,000 (21,877,000 were males and 23,367,000 females)

Marriages —In the 15–24 age-group, the proportion married has more than doubled since 1931 for both men and women Although total marriages were 7000 less than in 1957, the rates continued to rise slightly at the younger ages In 1954, 6 9% of bridegrooms and 28 6% of brides were minors, the corresponding figures for 1958 were 10 7% of bridegrooms and 35% of brides

Deaths —The crude death-rate—11 7 per 1000 persons of all ages—showed little change With allowance for population age-changes, the average reduction in mortality has been 60% in the past fifty years, and 40% in the past twenty-five years Between 15 and 24 years, the death-rate for males is more than double that for females, in this age-group seven times as many men as women die from accidents

Infant mortality —This continued to decrease deaths of children under 1 year numbered 22 5 per 1000 births in 1958, the lowest rate recorded till then Infant mortality as a whole has declined by two-thirds since 1928

Tuberculosis —There were 4480 deaths in 1958, compared with 19,797 in 1949 In the same time, annual notifications have declined from over 50,000 to 30,000

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[1] Registrar General's Statistical Review of England and Wales, 1958 Part III, Commentary H.M Stationery Office *Pp* 222 *13s*

Accidental and violent deaths.—These have increased progressively, the totals being 18,513 in 1949 and 22,456 in 1958. The increase is due mostly to increases in motor-vehicle accidents, accidental gas-poisoning, falls, and, in women only, suicide. The death-rate among men in the 15–24 age-group from motor-vehicle accidents increased from 26 per 100,000 population in 1954 to 35 in 1958. Accidental deaths attributed to barbiturate poisoning increased from 77 in 1949 to 205 in 1958, and to domestic gas from 421 to 870.

The September Quarter

In England and Wales in the September quarter, 1960, there were 197,572 live births, 3873 stillbirths, and 112,379 deaths.[1] The birth-rate (17.2 per 1000 population) was the highest for a September quarter since 1948, when the corresponding rate was 17.5. The stillbirth-rate was low—19.2 per 1000 live and still births.

Parliament

Professions Supplementary to Medicine Bill

THIS Bill received the Royal Assent on Oct. 27. Its provisions will not come into operation until they are brought into force by Orders in Council.

QUESTION TIME

Hospital Casualty Services

Earl WINTERTON asked the Government whether, in view of the criticisms made by an unofficial committee of the methods for dealing with casualty cases in National Health Service hospitals and of other evidence to the same effect, they would appoint a committee of inquiry.—Lord ST. OSWALD replied: My Lords, the Standing Medical Advisory Committee of the Central Health Services Council appointed, earlier this year, a subcommittee, under the chairmanship of Sir Harry Platt, to consider the organisation of hospital casualty and accident services and to make recommendations regarding their future development. The Scottish Health Services Council has set up a similar committee. I have no doubt that these committees will consider the recommendations made in the study, based on 20 casualty departments, which was recently published for the Nuffield Provincial Hospitals Trust.

Lord STONHAM: Is the noble Lord aware that, at the instance of the Minister, every regional board has been considering this problem, that they are proposing to concentrate major casualty centres in the hospitals in each group, but that what is needed is more money to equip, expand, and provide more casualty centres? And can he say whether that will be forthcoming?—Lord ST. OSWALD: I think that any decisions of that nature must naturally rest upon the finding of this subcommittee, which has been set up specifically for the purpose of discovering what the facts are, and of suggesting remedies.

Means Test for State Scholarships

Mrs. EIRENE WHITE asked the Minister of Education what decision had been reached on the recommendations of the Anderson Committee on parental means tests for university students.—Sir DAVID ECCLES replied: I shall very shortly announce a radical revision of the present means test, to be brought in by the autumn of 1961. This is without prejudice to the abolition of the means test if that, on full examination, should turn out to be required.

Smokeless Zones

On Oct. 1 there were 296 smokeless zones or smoke-control orders in operation in England and Wales, covering 255,974 premises, and 98 more smoke-control orders, covering 123,219 premises, have been confirmed but were not in operation. Some 1270 local authorities have not made smoke control orders, but most of these do not have a major problem of domestic smoke pollution.

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[1] Registrar General's Weekly Return no. 42, 1960. H.M. Stationery Office. Pp. 204. 1s. 6d.

Notes and News

WORLD HEALTH ORGANISATION

THE Director-General of W.H.O., Dr. M. G. Candau, and the retiring senior W.H.O. representative in the Congo, Dr. J. S. MacKenzie Pollock, have both reported on the medical situation there.

In July W.H.O. responded to a request by the Security Council, and within a week 28 staff members had been sent to the Congo. 28 medical teams provided by 25 national Red Cross societies answered a joint appeal by the League of Red Cross Societies and the International Committee of the Red Cross. These teams were initially to stay three months. Some countries offered additional assistance, and soon hospitals, not only in the cities, but in the country as well, were able to function again.

At each provincial capital, except that of Katanga, there is a W.H.O. group, consisting of a public-health adviser, a public-health engineer, and a mobile epidemiological team. These mobile teams have already begun to organise vaccination campaigns against smallpox, typhoid fever, yellow fever, and plague. To deal with these diseases and the other major health hazards—malaria, filariasis, leprosy, and tuberculosis—many staff members are being recruited. They will be paid out of the U.N. Congo fund and placed at the disposal of the Congo Government. The main need is to staff the district services with doctors who will superintend the hospitals and organise preventive health services. 130 health personnel are being recruited now, and this number will soon be increased to about 500. The Red Cross teams have been asked to remain for six months, or longer if possible.

The long-term problems can be solved only by training Congolese doctors. There are none at present, and the local university, Lovanium, will graduate only 2 in 1961, and not more than 19 in all by 1965. Dr. Candau considers that the 1959 situation cannot be regained in less than twelve to fifteen years. But an encouraging start has been made. W.H.O. is providing 13 additional teaching staff, including the first professor of public health, which has enabled Lovanium University to increase its medical-student intake to 40. The three schools for "medical assistants" will finish the six-year training of the present students and then close. All students after that will complete the full medical course at Lovanium University. 74 "medical assistants" are at present helping to provide essential health services.

Meanwhile 60 "medical assistants" have been awarded W.H.O. fellowships and have left for French medical schools to qualify as doctors after special two-year or three-year courses. 7 students with no previous training have been awarded fellowships for a full medical course in France or Switzerland.

Dr. A. Bellerive (Haiti) succeeds Dr. McKenzie Pollock as senior W.H.O. representative.

In Geneva, the 26th session of the Executive Board opened on Oct. 25. Dr. Henrique M. Penido (Brazil) was elected chairman.

THE WORLD'S FOOD

"Food and population are two of the crucial determinants of the future of mankind. Freedom from hunger in the less developed countries of the world, however, is not simply a matter of regaining or maintaining pre-war levels of per caput production and consumption. ... Much greater increases in food production in these regions are needed before any real progress can be made in stamping out hunger and malnutrition. But increased food production must go hand in hand with general economic development so that consumers can afford the additional food and the better quality food they need."

In these words, taken from his foreword to F.A.O.'s latest annual report,[1] the Director-General summarises the agricultural problem confronting the greater part of the human race. While the highly developed countries continue to increase production (to the point of accumulating surpluses) by

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[1] The State of Food and Agriculture 1960. F.A.O., Rome. Pp. 182. 10s. Obtainable from H.M. Stationery Office.

A Medical Staff Residence

On Oct 18, at Odstock Hospital, Salisbury, a new residence for medical staff was officially opened by Mr P G Templeman, chairman of the Wessex Regional Hospital Board

The residence has 17 bed sitting rooms each with its own wash-hand basin and built in furniture A large lounge is separated from the dining room by sliding doors and meals are served from a small service kitchen adjoining the dining room There is a library away from the living-room area Two flats for married residents have been built beside the new residence The flats are furnished and centrally heated, and each has a lounge/dining room, kitchen, main bedroom, and spare room The cost of the whole scheme, including furnishings, was £35,000

Award for Medical Film

La Presse Médicale is again offering a prize (1000 NF) for a medical 16 mm film whose time of projection does not exceed 30 minutes Films should be sent to the journal, 120, boulevard Saint-Germain, Paris VI^{e}, before Feb 1

Caloric Balance in Man

The Nutrition Society is to hold a symposium on this subject on Saturday, Dec 17, at the Middlesex Hospital Medical School, London, W 1 The speakers will be Dr J V G A Durnin, Dr O G Edholm, Dr Raymond Greene, Dr I M Chalmers, Dr G C Kennedy, Dr A M Thomson, Dr F E Hytten, and Dr E M Widdowson Further particulars may be had from the hon programmes secretary of the society, Miss D F Hollingsworth, c/o Ministry of Agriculture, Fisheries and Food, Great Westminster House, Horseferry Road, S W 1

A meeting of the Biochemical Society is to be held on Friday, Nov 18, at 10 A M, at the Middlesex Hospital Medical School, London, W 1, when there will be a colloquium on histochemistry

Professor J B Duguid, who has lately retired from the chair of pathology in the University of Durham, has left for Malaya, where he is to be an adviser in histopathology under the Technical Cooperation Scheme of the Colombo Plan

The Association of Universities of the British Commonwealth (36, Gordon Square, London, W C 1) have published a list of fellowships, scholarships, and grants tenable at universities in the United Kingdom and a short list of awards tenable outside the United Kingdom Copies are being sent to universities and libraries and to other institutions on request

A committee meeting of the Group for Representation of the Views of Clinical Psychiatrists will be held on Thursday, Nov 10, at 5 30 P M, at Tavistock House North, Tavistock Square, London, W C 1

The London Medical Exhibition will be held in the New Hall of the Royal Horticultural Society, Westminster, from Nov 11 to 18

University College London will hold a reunion dinner at the college on Friday, Feb 17, for undergraduates or postgraduates who entered before 1918 Early applications for invitations should be made to the assistant secretary of the college, Gower Street, W C 1

From Nov 21 the address of the National Council for the Unmarried Mother and Her Child will be 255, Kentish Town Road, London, N W 5

Film about Handicapped Children—The Cine Club of Bristol, with the help of the South Western Regional Hospital Board and the Bristol education and health committees, has produced *Claremont*, which shows how children with spastic disabilities are educated and treated at a school at Claremont, Bristol The film, which is in 16 mm colour, has a sound commentary and lasts about 12 minutes The hiring fee is 1 guinea Applications should be sent to the medical officer of health, central health clinic, Tower Hill, Bristol, 2

CORRIGENDUM *Treatment of Urticaria*—The dose of proguanil ('Paludrine') mentioned in Sir Charles Dodds' letter of Oct 22 should have been 0 1 g (100 mg)

Diary of the Week

NOV 6 TO 12

Monday, 7th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
1 P M Dr Brian Ackner Diagnosis of Depressive Illness

Tuesday, 8th

UNIVERSITY OF LONDON
5 P M (London Hospital Medical College, Turner Street, E 1) Dr Preston A Wade (Cornell University) Recent Advances in Fracture and Accident Services
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
5 30 P M *Experimental Medicine and Therapeutics* Dr A J Buller, Dr O C J Lippold Normal and Abnormal Willed Movement
8 P M *Psychiatry* Dr J J O Dwyer Dr Elliott Jaques Use of Psychiatric Skills in Industrial Organisations
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr W M Court Brown Chromosome Analysis and Clinical Medicine
ST MARY'S HOSPITAL MEDICAL SCHOOL, W 2
5 P M (Wright Fleming Institute) Mr D G Bonham Non malignant Enlargement of the Ovary
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr O L S Scott Anomalies of Pigmentation
MANCHESTER MEDICAL SOCIETY
8 P M (Clinical Sciences Building, York Place) *Surgery* Mr Ambrose Jolleys Treatment of Peripheral Tuberculous Glands Dr H B Andrews Tuberculous Glands
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M (General Infirmary at Leeds) Dr Paul Sandifer Involuntary Movements in Children

Wednesday, 9th

UNIVERSITY OF LONDON
5 30 P M (London School of Hygiene and Tropical Medicine) Dr Charles Wilcocks Aspects of Medical Investigation in Africa—Trypanosomiasis (Third Heath Clark lecture)
POSTGRADUATE MEDICAL SCHOOL
2 P M Dr P J Randle Regulation of Carbohydrate Metabolism by Hormones and Other Factors
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Skin Cancer
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr Paul Wood Present Position of Anticoagulant Therapy
MANCHESTER MEDICAL SOCIETY
5 P M (Medical School, University of Manchester) *Pathology* Dr Leon Poller Pathogenesis of Thrombosis
UNIVERSITY OF LEEDS
5 P M (General Infirmary at Leeds) Miss U M Lister Placenta
6 P M Mr T L Redman Inefficient Uterine Action
ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH, 9 Queen Street, Edinburgh
5 P M Lord Cohen of Birkenhead Changing Concepts of Diathesis in Medicine (Frederick Price lecture)

Thursday, 10th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W C 2
5 P M *Dr Wade Accident Surgery of Motorways* (Watson Jones lecture)
UNIVERSITY OF LONDON
5 30 P M (London School of Hygiene and Tropical Medicine) Dr Wilcocks Aspects of Medical Investigation in Africa—Implications (Last Heath Clark lecture)
ROYAL SOCIETY OF MEDICINE
5 P M *Ophthalmology and Dermatology* Dr G B Dowling, Dr J A Dudgeon Mr F S Perkins Behcet's Disease Dr I B Sneddon Mr Barrie Jones, Mr Frederick Ridley, Sir Benjamin Rycroft Bullous Conditions of the Skin and Conjunctiva
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Dr M R Pollock Physiological Adaptation in Micro organisms
ALFRED ADLER MEDICAL SOCIETY
8 P M (11, Chandos Street, W 1) Mr Lewis Way *Problems of Social Psychology*
CECIL GORDON LECTURE
5 P M (University New Buildings, Teviot Place, Edinburgh) Prof Lancelot Hogben Nature Nurture Issue and the Medical Curriculum
HONYMAN GILLESPIE LECTURE
5 P M (University New Buildings, Teviot Place, Edinburgh) Mr J H S Scott Accident Services
UNIVERSITY OF ST ANDREWS
5 P M (Physiology Department, Queen's College, Dundee) Prof M F A Woodruff Outlook for Transplantation of the Kidney in Man

Friday, 11th

POSTGRADUATE MEDICAL SCHOOL
10 A M Mr A J C Latchmore Surgery of the Biliary Tract
1 P M Prof W S Peart Ischaemic Kidneys in Hypertension
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330 Gray's Inn Road, W C 1
3 30 P M Dr D A Osborn Disorders of the Blood in E N T Practice

Appointments

BOYD, J M, M B Glasg, D P H depute M O H, Renfrewshire
BARLOW, A R, M B Lond, D I H, D C H, D T M & H divisional M O Bedfordshire
GRAHAM, P A, M B Glasg, F R C S consultant ophthalmologist, United Cardiff Hospitals and Welsh Regional Board Hospitals
HAINES, CICELY R, M B Sheff, D OBST assistant M O H and school M O Bournemouth
SPENCER, P M, M B Lond, F R C S, M R C O G, D OBST consultant obstetrician and gynæcologist Elizabeth Garrett Anderson Hospital London
THOMSON, R B, M D Durh, M R C P consultant physician Royal Victoria Infirmary Newcastle upon Tyne
TURNER WARWICK, MARGARET E H, D M Oxon, M R C P consultant general physician Elizabeth Garrett Anderson Hospital London
WRIGHT, D G, M B Glas, F R C S E consultant orthopædic surgeon Durham group of hospitals

The Lancet · Saturday 12 November 1960

PREPARATION FOR THE PROFESSION *

The Present and the Future

JOHN ELLIS
M B E , M A , M D Cantab , F R C P
PHYSICIAN TO THE LONDON HOSPITAL, LONDON, E 1, AND TO THE PRINCE OF WALES GENERAL HOSPITAL, SECRETARY TO THE ASSOCIATION FOR THE STUDY OF MEDICAL EDUCATION

THERE are periods in the history of every country when the form of medical education is appropriate to the pattern of medical practice, and when that pattern is itself suitable to the medicine of the day, so that all knowledge can be applied effectively and ethically The standard of medicine is then as high as the degree of knowledge will allow, for medicine is in balance

Such a period comes to an end when there is a major advance in medical knowledge This advance passes very rapidly into practice and changes the pattern of it The change of practice then alters medical education, and if all goes well balance is restored

It is our particular good fortune to belong to medicine when it is again changing, or to be accurate has just changed The increase of knowledge has enforced specialisation—which itself ensures that knowledge will continue to grow at speed But, because in Britain no-one now lives far from a specialist, the general practitioner is prevented from doing much of the therapeutic job he was trained for Instead, he is left with an overwhelming amount of other problems of diagnosis, treatment, and prevention of disease, for which he was not trained He must transfer many patients to the care of another doctor, and he must be sure that he chooses the right specialty

While this increase in knowledge has thus been altering the pattern of practice, a change in the quality of knowledge has altered the doctor's concept of disease His attitude to diagnosis and treatment has become more scientific

But it must be noted that the change is in attitude to disease and not in attitude to the patient The problem of medical education is how to inculcate the scientific attitude while maintaining the highest standard of clinical skill and the most humanitarian concern for the patient as a person

* * *

It took us quite a long time to accept that with the coming of specialisation had come the end of general practice as we knew it, and also the end of the apprenticeship training which it had evolved for itself During that time an inevitable disruption of medical education has been intensified, more in some schools than others, by our continuing to produce general practitioners of a kind no longer required, by a system of apprenticeship to specialists which could not be successful anyway

However, that era of uncertainty as to the aims and objects of medical education is over It ended, in fact, several years ago when the General Medical Council in its *Recommendations* of May, 1957, officially stated that the aim is no longer to produce, by the time of qualification, a finished doctor of any kind In future medical education, for family doctors as well as for specialists, is to consist of two portions, undergraduate and postgraduate The significance of this radical change has not yet been fully appreciated for several reasons One is that a year of internship after qualification had become compulsory before 1957, and therefore the G M C 's action appeared to some to be no more than giving official blessing to something which had already happened A second is that, because medical education in this country is very rarely the primary concern of anyone, very many of those actively engaged in it have not yet read the G M C 's recommendations A third is that, in contrast to all its previous announcements the G M C did not specify in detail the nature of either a minimum undergraduate education or a minimum postgraduate training It very wisely left the onus of creating a new pattern of undergraduate education to each individual university and medical school, stating that this pattern must provide a sound basis for further study, by ensuring that the student not only acquires knowledge and clinical skill but also scientific method, he is to be given an education as well as a training This freedom is obviously essential if each of our 26 schools is to be able to develop new enterprise to the best of its capabilities, but initially of course it can act as a stimulus to progress only in those schools where the desire for progress exists

Thus, though medical education in this country has passed out of the phase of catabolism into the phase of anabolism, the signs of this are not to be seen in every university Some schools have set a new course for a new educational objective and are under way, some are drifting out of control, some are in the doldrums, and some are being blown far off course—even off their original course—by the contrary winds of contemporary medical practice It is inevitable that some will have a greater proportion of teachers who are firmly attached to the old form of training, but it is equally inevitable that these teachers, by their resistance to change, will demolish the pattern they seek to preserve It is natural that those schools which have been most successful in the application of one method should be the last to realise that it does not work any more The man who has for years travelled to his destination in a Rolls-Royce does not think of getting rid of it—until he discovers that others are getting there more satisfactorily in an aeroplane—with Rolls-Royce engines, of course

There is therefore cause for neither surprise nor lament in our present state of medical education, save in one respect Speed of adaption is obviously important and it does appear that this could be unnecessarily slowed in London About half of our medical students receive at least their clinical training in the 12 London medical schools Inequitable as it may seem, a faculty which has 12 separate schools is unable to move 12 times as fast as other universities, and is more likely to resemble a convoy whose speed is always that of the slowest ship It is always difficult for the commodore of a convoy to give the order " All ships to proceed at their best speed " It is true that in this case precisely that order has been given to the whole medical-education navy by the G M C , but there is in this country a well-known precedent for turning a blind eye to the receipt of a naval signal

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* Extracts from the Wood-Jones lecture delivered in the University of Manchester Medical School on Feb 9, 1960 An abridged version of the lecture appears in the October issue of the *Manchester Medical Gazette*

However, all schools have been charged with the duty of adapting their education to meet modern conditions and needs, and most have already begun to do this.

At first sight they appear to be up against an insuperable difficulty—that of deciding how much knowledge and how much training is to be in the undergraduate years, and how much in the postgraduate. These questions seem difficult to answer in view of the fact that the responsibility for the postgraduate years is shared by the university with many other organisations, including the Royal Colleges and the Ministry of Health, and no one of them has sole authority. Furthermore, nobody could at the moment be precise as to how much knowledge and how much technical skill is necessary for the minimum effective practice of any branch of medicine, particularly as the function of the family doctor is not yet clearly defined.

But the fact that we do not know these things need not inhibit the reform of undergraduate education at all. For the aim of this, now, is first and foremost to *educate*—i.e., to give the student *not* knowledge but the power to utilise knowledge.

That he must know facts is obvious, and that in his early days he cannot find these out for himself but must be given them is equally obvious. His and his teachers' primary purpose, however, must be that he learns how to learn for himself. Therefore the factual content of the undergraduate period does not have to be any particular percentage of the total of medical knowledge, it has to be chosen for its relevance to future learning, not for its relevance to future practice. Equally important, the student's progress must be assessed *primarily* on his ability to reason and utilise knowledge, and not merely in terms of the amount he knows. Similarly his clinical proficiency must be judged on the soundness of his method, of which the correctness of the physical signs he elicits from a patient in an examination is but one indication. By the same token, if it be true, as is sometimes claimed, that the newly qualified of today know more than their predecessors ever did, this does not mean that all is really well with medical education.

If the object of undergraduate education is achieved, then gaps in knowledge and inadequacy of technique will be made good in the postgraduate period. If the object of undergraduate education is not achieved, then such gaps will probably remain for ever, and he will be largely denied the mastery of new data and the critical evaluation of new treatment. Though specialisation has come to stay, there is nothing the least static about the size or form of any particular specialty. The future happiness and success of specialist and general practitioner alike depend on his ability to learn and on his knowledge of general principles.

The following should be our objectives:

1. The student must learn how to learn for himself.
2. He must acquire a scientific method of thought—i.e., the power to reason and think critically.
3. He must achieve competence in clinical method—i.e., the techniques of obtaining information from patients.
4. He must gain an understanding of the responsibilities of a professional person.

If these objectives are reached the student will inevitably have built up a foundation of knowledge, including empirical knowledge. He will also have built a foundation of clinical experience, as regards the diagnosis, treatment, and prevention of disease on the one hand and the nature of man on the other. The exact content of the foundations of knowledge and experience will vary, but during the years of his postgraduate training, each student will be able to fill in those gaps relevant to his own future practice.

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The undergraduate course of studies, thus freed from the need to include all or even any fixed percentage of knowledge and technique, can now, and must now, be based on considerations of the processes of learning.

This granted, it is at once evident that many different arrangements of studies have much to commend them in theory. Until they have been tried in practice, there can be no way of judging between them, and in any case the judgment can be no more than a clinical one. It is therefore idle to speak of the curriculum as though there is somewhere a correct arrangement which will be correct for every school and every student. The best curriculum for any particular school is that which enables it to make the best educational use of all its facilities and enables its students to progress through successive stages of learning, each with a clearly defined objective.

The number and sequence of stages, together with the purpose and content of each, will vary from school to school, but there are certain requirements which must be met in every stage everywhere:

1. Its purpose must be equally clear to both teachers and taught.
2. There must be deployed in it those incentives to study which are relevant to that purpose.
3. There must be built into it such forms of assessment of the student's progress as are appropriate to its content.

It goes without saying that other objectives, contrary incentives, and inappropriate tests should be excluded as rigidly as possible.

A course of studies of this kind cannot be made by a mere alteration of the timetable, even if this is done with educational objectives in mind. An entirely new attitude to teaching is required, and reform of the curriculum will be ineffectual unless there is also a reform of the method by which the curriculum is devised, applied, and constantly assessed. In my opinion this is no longer a matter of administration from the dean's office. There is required for each stage of the course a team of men who are responsible for it. They should represent all those departments most closely concerned with that stage, together with others whose advice could be helpful, even if they are not likely to teach in it themselves. For example, preclinical teachers should be concerned with the planning and assessment of predominantly clinical stages, and clinicians with the predominantly preclinical stages.

The team should, moreover, be representative of whole-time and part-time teachers, thus ensuring that the largest possible number of all kinds of teacher are closely involved in the educational effort. In this way cooperation can be achieved, for, instead of every department competing for what it feels is its rightful portion of the student's time, each becomes more concerned with what it has to contribute to the common purpose of each stage of the student's development. Furthermore, it is only when a teacher is able to appreciate the overall picture of that development that he can judge at what stage his own subject can make its best contribution. At present the resources of a special department are often squandered because students are routed through it too early or too late. Frequently also a student is able to attend a department for one period only, although it has something to offer him at several stages.

The effective planning, execution, and frequent assessment of every stage of a real course of studies is quite beyond the capabilities of any dean's staff or curriculum committee, but every school could muster a team for each stage Each team would be working towards a comprehensible and realisable objective, and would be able to define the content of knowledge and practical experience, deploy relevant incentives, and devise appropriate forms of assessment If integration of staff were ensured, the student would be helped to integrate his knowledge for himself without the aid of elaborate timetable innovations —and neither the autonomy of departments nor the freedom of individual teachers would be lost

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Later stages must of course continue to be based upon existing firms and departments, but the great strength of these will be fully utilised if all concerned know what they are trying to do For example, a stage devoted to practice of clinical method must obviously use general inpatient firms, but the teachers on these firms would not be left, as now, to try to grapple with all aspects of medicine, and would have instead agreed limited objectives together with a chance to assess their results Nor would they have to contend and compete with synchronous courses of instruction, of which neither the content nor the purpose was known to them

It is in the later part of the present clinical curriculum that confusion and dissipation of effort are now so marked, particularly in regard to the purposes of outpatient experience and the contribution of special departments Order can be created again out of near-chaos by this simple process of organising stages of learning and experience by groups of teachers responsible for them

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Our peculiar system of hospital staff structure has provided us with a teaching device in the firm, which ensures that a small number of students are closely attached to a teacher who is personally responsible for them and for the patients with whom they are concerned The student is thus constantly reminded that the care of the individual patient is the yardstick by which everything else is measured He is able to learn of the professional responsibilities of a doctor by the only possible method—observing the doctor fulfilling them Above all, the welding together of his education and practical training is assisted by his being required to focus both his integrated knowledge and his practical skill upon the problems of his patients He is enabled to acquire empirical knowledge and experience and at the same time be encouraged to learn scientific method because his teacher can set him this example, can excite his curiosity, and can guide him as an individual through his personal difficulties of learning

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At this stage it should also be easy to extend the student's experiences outside the walls of the hospital, to give him an understanding of the patient as a whole, and demonstrate the relation of medicine to the community It is here that I would incorporate the general practitioner into the undergraduate teaching team, with membership of the committee responsible for this stage, so that he is conversant with the objectives which the student has been set and with the lines on which his development is planned

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The provision of a new curriculum and a new type of administration, however, will not completely solve the problem of readapting medical education to present conditions of medicine The inclusion into undergraduate medical schools of all that is meant by university education is also necessary An essential requirement of this is interest in the individual student, so that he may develop in a stimulating intellectual atmosphere, with the encouragement and guidance of his teachers It would be idle to pretend that this is now possible in all our schools

If the medical student is to be a university student, then he must be treated as such, and the medical school must provide not merely teachers, a curriculum of classes, and an administration, but also an educational service It is not enough to have a tutorial system which is a mere adjunct to the other forms of teaching The system providing encouragement and guidance must not be separate from the system of reproof, which is represented by authority and vested in the dean Any dichotomy can only result in resentment of authority or frustration of encouragement But if all good incentives are mobilised and coordinated into one discipline, then progressive assessment of the individual becomes possible, and he can be given such help as he is known to need The medical school must have some kind of director of studies as well as a dean—just as our older university colleges have a senior tutor as well as a master—tutors and supervisors as well as teachers

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I believe that part of the last clinical year should be devoted to a stage of learning by experience under supervision, and that this should be based on attachment, for at least four months to a general medical firm, primarily in the outpatient department but extending into the wards. In this students should be responsible for individual patients as they now are on the traditional inpatient firm. Student and patient together would visit the special departments as the patient's condition demanded, and both would return to the doctor responsible for both.

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The increased need for education requires also a new attitude to halls of residence. In many universities these have long been recognised as a means whereby students can educate themselves by indirect contact with several faculties. In his later years, however, the medical student lingers on after his colleagues in other disciplines and tends to become more attached to a hospital than a university. Those who have no home in the vicinity may live in a hostel belonging to the medical school, but such hostels, as their name implies, are often thought of as merely lodging-houses conveniently near the wards. There is a great need for a change of attitude so that these places can play their full part in education. All students should spend some time in them, and not merely those who have difficulty in finding accommodation elsewhere. Far greater responsibility for the corporate life of the student body should then be given to the students themselves—a necessary experience for those who are going to carry heavy professional burdens but who now tend to be kept from both responsibility and community life up to the age of 24. In this field also the teaching staff have a large part to play, not as persons of authority or with administrative duties, but as senior members of a single professional and intellectual community.

In none of these things, which I believe to be so important, do I envisage any kind of spoon-feeding or wet-nursing of students. On the contrary, I am advocating that they be regarded much less as groups of overgrown schoolboys, and much more as individual adult members of a profession. Their reactions to the education offered must be regularly sought, as in most other countries it now is, and they should feel free to seek advice on problems of learning without fear of jeopardising their careers. In the past medical schools have been so concerned with teaching and examinations, that few facilities, either material or in personnel, now exist for education. The need for them is urgent, and they are required for the postgraduate as well as the undergraduate. The days have passed when any medical school can feel that its responsibility for a man has ended when he has passed his final examinations.

" Finals ", of course, are now a misnomer, for they merely indicate a qualification which is necessary before the student is in his last year of general internship, legally able to undertake the responsible practice under supervision of which this stage of experience is composed. It remains to be seen whether this stage should be increased in duration or advanced in time. But it is already a responsibility of the medical schools, though not one which they have been able fully to discharge. They will need to develop a much more active system of caring for the individual before they can do so.

It will only be when such a system has developed that many other features of a university education in medicine can be properly undertaken. For example electives, and opportunities for students to study a subject in depth by undertaking some piece of original work, depend for their full effect on adequate knowledge and guidance of the individual. Furthermore we have to regain in this country greater freedom for each student to develop in his own way and at his own speed. We have had an overcrowded curriculum for so long, that we have almost come at accept the idea of having the same timetable for every student. Worse still, the system of grants, by which most students are financed, has encouraged the idea, in both medical schools and grant-giving authorities, that there is a fixed maximum duration of studies which is properly common to all students. This is most unfortunate, because no-one has ever laid down more than a minimum period, and students do not all progress at the same speed. It is an odd paradox that by so rightly removing financial barriers to medical education in this country, we have at the same time removed from the individual his necessary freedom to vary from the average. In the United States where most students are privately financed, it is easier for a man to step off the production-line than it is here, where courses are repeated only by students who have done badly. In Sweden, where students can get State loans but not grants, the finishing line is an entirely personal affair. Our system of a class of students all taking their examination on the same day is regarded as most unusual.

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In my view readaptation of medical education depends then, on (1) a course of studies, based on stages of learning together with relevant forms of assessment, (2) a more effective method of operating and maintaining the new curriculum, and (3) a university atmosphere. If these three things are provided, then undoubtedly new teaching techniques will emerge, or at all events we shall learn much more than we now know about the problems of education and the answers to them. In order to set our house in order, however, we do not need any more information than we now have. It is as useless as it is dangerous to wait for scientific proof that this or that is necessary, or that one scheme is better than another. This is a matter for clinical judgment. It is futile, and really only a form of escapism, to wait for some magic concrete plan which can be put into administrative effect and then forgotten.

The main obstacle to the full implementation of these three things is that very few teachers have enough time in which to give undivided attention to education. This can be remedied only by ensuring that part-time clinical teachers particularly, have enough sessions at the teaching hospital to enable them to practise clinical medicine, educate students, and engage in research. It is essential that this is done, if the country is to continue to have a high standard of medical service. It will inevitably cost money, but medical education is important. It alone can pass the advances of medicine on into effective practice. It is hopeless and wasteful to tackle it halfheartedly, and the most economical medical school, like the most economical hospital, is the one which sets out to be the best rather than the cheapest.

If in the National Health Service we can but make the terms and conditions of service of medical teachers relevant to the demands of education, we shall be able to mobilise a quite remarkable number of assets. Indeed, we should be in a far better position than any other country to solve the remaining problems of medical education.

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It seems justifiable to expect, therefore, that after a long period of difficulty, we can now enter a period in which medical education will be once more in equilibrium with medicine. Certainly we should be able most successfully to give an education in medicine while retaining and even improving our ability to teach sound clinical method. But this does not mean that we will then be automatically giving a good preparation for medicine as a profession.

The basis of British practice is that each patient, whether in his home or at hospital, has one doctor who takes personal responsibility for him, but there is no doubt that this basis has been weakened, and that too often there is uncertainty as to who is really responsible for the patient. The doctor also has a responsibility to the community, which cannot be discharged merely by attending to individuals, and students have to be made aware of very many important duties of the profession other than that of diagnosing and treating disease. Lastly we have, always, the problem of the way in which we discharge our duties—the standard which the profession sets for itself and the nature of its corporate discipline.

In times of great change the standards of a profession are at risk, and all ethics have to be translated into new terms. Moral exhortation without content or direction is a futile thing, and today the student must be brought to share the problems which face his teacher both as concern the patient and the profession. He must learn that science, which he must use, searches only after truth and has no humanitarian ends in view, but he must also learn that in a *professional* community, unlike others, how a decision is made is more important than what is decided.

These problems are difficult—but only because medicine and the profession face a greater challenge than ever before. I would say that there has never been a better time than this in which to be a doctor: the opportunities, like the challenge, are greater than ever before. They are greater, I believe, in this country than in any other: we are in a better position to solve all our problems. But we cannot do so unless we set our sights high. We must accept that in a time of change the most idealistic approach is the most realistic. The pursuit of quality is the only aim proper to our profession and the only one it can afford to have.

THE EFFECT OF TEST FEEDS ON THE PLASMA LIPIDS

K. J. KINGSBURY
M.B., Ph.D. Lond.
SENIOR LECTURER

D. M. MORGAN
RESEARCH ASSISTANT

P. C. SHERRINGTON
RESEARCH ASSISTANT

THE SURGICAL UNIT, ST. MARY'S HOSPITAL, LONDON, W.2

IT has been shown repeatedly that the type of fat in the diet affects the lipid content of the plasma. But the kind of investigation so far reported has several disadvantages.

The lipid changes have been produced by feeding particular oils and fats for several days, weeks, or even months, with the remainder of the diet under careful control, and in these circumstances several weeks elapse before the plasma lipids reach a constant level on the basal diet and again with each fat under test. Because during all this time the basal diet has to be rigidly controlled (Ahrens et al. 1957), many investigators have resorted to giving this diet as homogenised liquid feeds (Kinsell et al. 1953). Apart from the practical difficulties—especially for studies on normal people and outpatients—arising from long-continued control, the test materials may not be available in sufficient quantity, or may be unsuitable for long-term administration (e.g., tung oil). Moreover the effects of trace materials, and the relative importance of particular substances, are often difficult to evaluate when whole diets are being fed.

Hence, for identifying and defining the dietary factors that influence human lipid metabolism, there is need of a quick and reproducible biological test. This should last no more than 12 hours, for then only the test substance need be fed, the experimental conditions can be easily controlled, and any lipid changes can be compared with the effects of fasting for an equal period. Also, if the test is to be used as a method of biological assay, it should evoke reproducible responses in normal people and be sensitive to small changes.

Such a method, in this laboratory, has been in use for 4 years. Single test feeds of oils are given under standard conditions so that the effect of each oil on the plasma lipids can be quickly and clearly demonstrated. In this paper we illustrate the method first by describing the effect of arachis oil on the plasma glyceride, phospholipid, and cholesterol, and then by reporting the effects of various other oils.

Materials and Methods

The subjects were healthy male medical students (aged 19–33) on the same kind of diet and activity. They were not allowed dietary fat during the 12 hours before the experiment nor excessive fat on the previous day, and their fasting plasma was clear. A light breakfast of fat-free drinks, dry toast, and marmalade was allowed 2-3 hours before the experiment.

The Test Feed

50 g of the oil is given as a single feed, emulsified with 50 ml of skimmed milk and 50–100 ml of tap water, and flavoured if desired. (With feeds of less than 30 g the changes in the plasma lipids are small and inconsistent, while feeds above 60–70 g often cause nausea without proportionately increasing the plasma-lipid changes.) The emulsions must not be oily or thick and should be at room temperature; they should be drunk quickly, without breathing through the nose. The feeds are followed immediately by a strong-tasting drink, such as black-currant cordial, and by an apple.

A standard procedure without unpleasantness is essential, for, if the subjects are nauseated, the absorption of the feed is apparently delayed and the plasma-lipid changes are prolonged and inconsistent.

Collection of Blood Samples

Samples were taken before the feeds, and at 1½, 3½, 5½, 7–9, and 24 hours after them. The blood was obtained by venepuncture using siliconed syringes and run into 3.8% sodium-citrate solution buffered to pH 7.4 (18 ml of blood to 2 ml citrate solution), the plasma was separated immediately by centrifuging and then stored at 4°C. The analyses were begun next day.

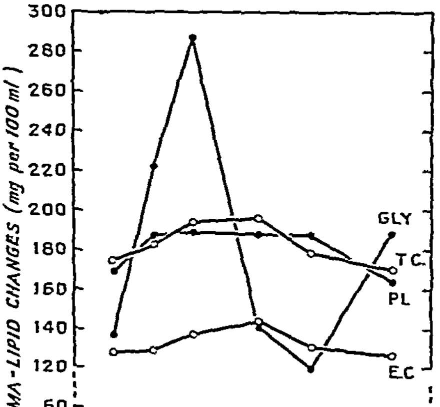

Fig. 1—The plasma-lipid levels before and after the 50 g meals of arachis oil (mean of six results).

GLY., glycerides; T.C., total cholesterol; PL., phospholipids; E.C., esterified cholesterol; F.C., free cholesterol; U.F.A., unsaturated fatty acids.

Methods of Analysis

Lipid phosphorus was determined by the method of Fiske and Subbarow (Hawk et al 1947), total and free cholesterol by that of MacIntyre and Ralston (1954), unesterified fatty acids according to Grossman et al (1954), and plasma total esterified fatty acids by the method of Morgan and Kingsbury (1959)

The entire series of plasma samples from each individual, plus the various standards, were analysed together in triplicate In this way fine differences between samples could be recognised The coefficient of variation of replicate samples by each method has always been less than 0 8% Total-cholesterol or *phospholipid changes of more than 3 mg per 100 ml* between the samples of one run, have therefore been accepted as significant

Effects of Arachis Oil

After single feeds of 50 g arachis oil the first observed change in the plasma lipids was an increase of glycerides, which reached a maximum 3–3$^{1}/_{2}$ hours after the feeds, after which the values fell rapidly for 3 hours and then more slowly and variably This increase in glycerides was accompanied by a slower rise and fall of the plasma cholesterol, phospholipids, and unesterified fatty acids, which reached their maximum at 3–6 hours after the meals, decreased gradually in the next 3 hours, and then fell very slowly The amount and the timing of the cholesterol and phospholipid changes were very similar The behaviour of the plasma lipids is shown in fig 1, which gives the average values obtained in six volunteers

It has been found that if too little of the oil is absorbed, or if the oil is absorbed too slowly, the subsequent changes in the cholesterol and phospholipids are inconsistent and unpredictable Adequate absorption of the oil, normally timed, is therefore a necessary condition of the experiment, and we do not consider it adequate unless the plasma glycerides rise between the fasting and $3^{1}/$ -hour samples and fall between the 3$^{1}/_{2}$-hour and $5^{1}/$ -hour samples Thus, if the plasma glycerides had not increased by more than 60 mg per 100 ml plasma (0 7 mMol per litre) at 3$^{1}/_{2}$ hours, and if over a third of this increase had not been removed by 5$^{1}/_{2}$ hours, the experiment was rejected The glyceride increases shown in our results represent, therefore, the differences between the fasting and 3$^{1}/_{2}$ hour samples, and the percentage clearances are the percentage removal of these increases between $3^{1}/$ hours and 5$^{1}/_{2}$ hours

In normal subjects with a clear fasting plasma and a

CHANGES IN PLASMA-LIPID LEVELS CAUSED BY SINGLE FEEDS OF VARIOUS OILS

Type and number of feeds	Plasma-lipid changes (mg per 100 ml) average and range									Fig 2 no	Iodine value of oil
	Glycerides		PL	T C	F C	E C	T C /PL	F C /E C	U F A		
	Increase	Decrease									
Group 1 Coconut (6)	144 *(106–257)*	46% *(38–62)*	23 *(20–25)*	27 *(24–29)*	11 *(9–12)*	16 *(15–17)*	1 12 *(0 96–1 4)*	0 69 *0 53–0 80*	17 *(14–24)*	1	8
Palm (4)	134 *(64–182)*	52% *(48–65)*	20 *(18–24)*	21 *(18–24)*	8 *(5–10)*	13 *(10–15)*	1 05 *(0 80–1 2)*	0 61 *(0 40–0 66)*	16 *(15–19)*	2 2	52
Arachis (18)	143 *(81–210)*	57% *(51–65)*	20 *(16–26)*	20 *(16–24)*	7 *(5–8)*	13 *(12–15)*	1 00 *(0 84–1 20)*	0 54 *(0 33–0 58)*	20 *(14–28)*	3	89
Olive (6)	179 *(123–234)*	50% *(42–56)*	21 *(19–24)*	19 *(18–22)*	6 *(5–9)*	13 *(12–15)*	0 91 *(0 85–1 1)*	0 46 *(0 38–0 59)*	19 *(15–26)*	4	83
Tung (2)	90 *(64–116)*	42% *(38–49)*	17 *(14–21)*	18 *(15–22)*	5 *(4–6)*	13 *(11–6)*	1 1 *(1 1)*	0 38 *(0 38–0 37)*	14 *(13–14)*	5	165
Group 2 Sunflower (5)	172 *(110–197)*	63% *(49–72)*	12 *(10–14)*	7 *(6–8)*	2 *(2–3)*	5 *(4–7)*	0 58 *(0 56–0 68)*	0 4 *(0 36–0 68)*	24 *(19–31)*	6	131
Safflower (3)	146 *(92–216)*	48% *(41–53)*	13 *(9–16)*	6 *(5–8)*	2 *(2–3)*	4 *(3–6)*	0 52 *(0 5–0 55)*	0 50 *(0 33–0 66)*	19 (12–28)	7	138
Corn (4)	138 *(103–157)*	51% *(41–62)*	14 *(11–15)*	6 *(4–8)*	2 *(2–3)*	4 *(3–5)*	0 43 *(0 4–0 65)*	0 50 *(0 4–0 7)*	21 *(19–26)*	8	113
Soya (2)	118 *(122–114)*	44% *(36–52)*	14 *(14–15)*	8 *(7–9)*	3 *(3)*	5 *(4–6)*	0 57 *(0 5–0 6*	0 60 *(0 5–0 75)*	21 *(17–25)*	9	134
Cotton-seed (2)	141 *(112–170)*	48% *(40–51)*	14 *(14–15)*	9 *(9–10)*	3 *(3)*	6 *(6–7)*	0 66 *(0 6–0 7)*	0 50 *(0 4–0 6)*	16 *(17–15)*	10	106
Whale (6)	166 *(100–158)*	68% *(53–79)*	14 *(12–16)*	6 *(4–8)*	2 *(1–3)*	4 *(3–5)*	0 48 *(0 4–0 58)*	0 5 *(0 36–0 64)*	21 *(11–28)*	11	128
Pilchard (3)	125 *(106–139)*	53% *(38–67)*	15 *(12–17)*	8 *(7–10)*	3 *(3–4)*	5 *(3–7)*	0 54 *(0 47–0 57)*	0 6 *(0 5–0 6)*	15 *(13–23)*	12	152
Heated tobacco seed (12)	160 *(64–256)*	56° *(45–59)*	10 *(5–15)*	5 *(2–10)*	1 *(0–3)*	4 *(2–8)*	0 50 *(0 21–0 57)*	0 25 *(0 0–0 6)*	20 *(12–26)*	13	136
Group 3 Stored crude tobacco-seed (12)	145 *(99–204)*	61° *(43–67)*	10 *(5–13)*	2 0 *(0–6)*	−3 0 *(−1–−6)*	5 0 *(2–10)*	0 20 *(0–0 7)*	−0 6 *(−1 2–−0 2)*	19 *(13–24)*	14	136
Crude tobacco seed (12)	188 *(72–470)*	62° *(49–78)*	0 25 *−5–−5*	1 *(−3–+3)*	−8 0 *(−3–20)*	9 *(+3–+20)*	4 0 *(−0 75–−2 0)*	−0 9 *(−0 8–−1 1)*	19 *(12–39)*	15	136
Fasting (12)	−24 *(+1–−68)*		−5 *(−2–−10)*	−6 *(−1–18)*	−3 *(−2–−4)*	−3 *(−1–−9)*	1 2 *(−0 66–+3 0)*	1 0 *(+0 2–+3 0)*	−3 *(+3–10)*	Not included in Fig 3	
Fraction A (2)	123 *(116–130)*	48° *(39–57)*	9 *(7–11)*	2 *(0–4)*	−2 *(−1–−3)*	4 *(1–7)*	0 2 *(0–−0 3)*	−0 5 *(−1 0–0 4)*	16 *(15–18)*		
Fraction B (2)	161 *(135–177)*	56° *(47–65)*	12 0 *(9–15)*	7 *(6–7)*	2 0 *(1–3)*	5 *(5–4)*	0 58 *(0 66–0 47)*	0 4 *(0 2–0 75)*	25 *(16–34)*		
Cod liver (2)	101 *(19–113)*	62 *(48–76)*	13 *(11–15)*	8 *(5–11)*	3 *(2–4)*	5 *(3–7)*	0 61 *(0 45–0 73)*	0 6 *(0 7–0 57)*	30 *(21–39)*		150

PL = Phospholipids T C. Total cholesterol F C = Free cholesterol E.C = Esterified cholesterol U F A = Unsaturated fatty acids

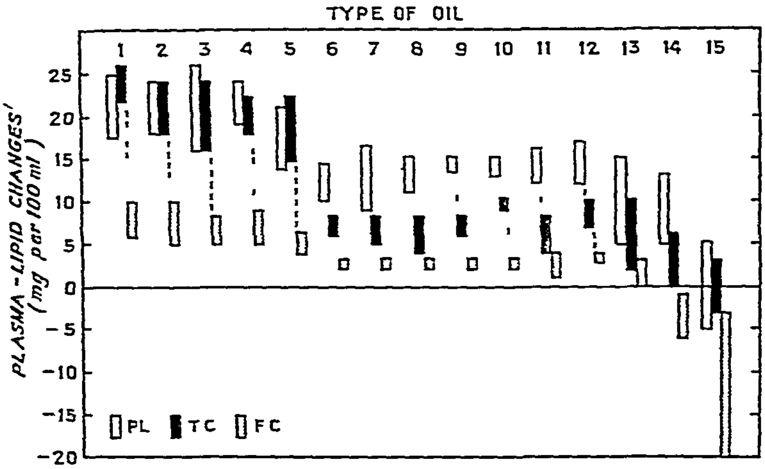

Fig 2

Fig 2—The changes in plasma phospholipid and cholesterol caused by the various oils (numbered as in table)

The effects of fractions A and B, cod-liver oil and of fasting, shown in the table are, for the sake of simplicity, not included in the figure.

PL.=phospholipids, T C.=total cholesterol, F C.=free cholesterol

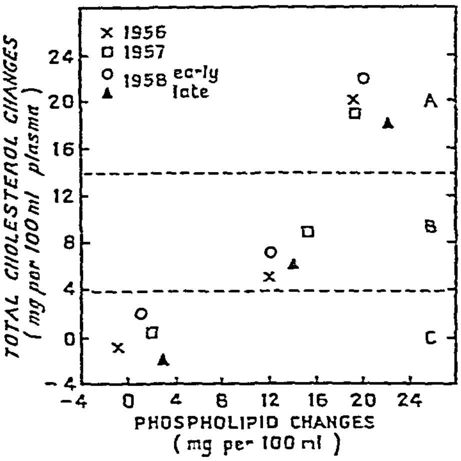

Fig 3

Fig 3—The response of three subjects to the same test feed when fed at intervals over 3 years

A, arachis, B, heated tobacco-seed oil, C, crude tobacco-seed oil The fasting plasma levels of the three subjects were A, phospholipids 98 mg per 100 ml, total cholesterol 235 mg, B, phospholipids 158 mg, total cholesterol 169 mg, C, phospholipids 222 mg, total cholesterol 254 mg

normal absorption of glyceride, plasma cholesterol and phospholipid reached their maximum 3–6 hours after the feed. The changes in phospholipids and cholesterol caused by the feeds can be expressed by the values

$$\frac{(3^1/_2\text{ hour}-\text{fasting})-(5^1/_2\text{ hour}-\text{fasting})}{2}$$

The figure obtained in this way we call the lipid response.

Effects of Various Other Oils

Single 50 g feeds of other oils were fed in the same way to normal volunteers The oils used, the number of experiments, and the lipid response are shown in the table.

Non-polymerised refined tung oil was supplied by Unilever Co The other oils were of edible grade and obtained from Unilever Co, H M Faure & Co, British Cod Liver Oils Ltd, and through Hess Products and Cyclo Chemicals Ltd

“Stored tobacco-seed oil” is crude oil which has been stored at 4 C in the dark for 9 months and ‘ heated tobacco-seed oil ’ is the crude oil heated by steam to 165 C under a high vacuum

“Fraction A” and “fraction B” were prepared from the fatty acids obtained by dehydrating ricinoleic acid Those liquid below 10 C (Hilditch 1956) were stored at 0 C for several weeks in the dark in an atmosphere of nitrogen, a solid fraction was separated by filtration at 0 C Both liquid and soil fractions were then frozen at 20 C, stored at 0 C for several weeks, and filtered as before The fractions solid at 0 C were combined and called fraction A, the combined fractions were called fraction C They were fed as ethyl esters

With all the oils, plasma glyceride rose by more than 60 mg per 100 ml and over a third of this increase was removed at $3^1/_2$–$5^1/_2$ hours But the different oils produced three different types of lipid response, and can accordingly be placed in three groups (table and fig 2)

Group 1—These raised the total-cholesterol and phospholipid levels by about 20 mg per 100 ml., without altering the ratios of total cholesterol to phospholipid or of free cholesterol to esterified cholesterol.

Group 2—The increases in total cholesterol and phospholipid were smaller, but the ratio of total cholesterol to phospholipid was reduced. The ratio of free cholesterol to esterified cholesterol was unaltered.

Group 3—With the oils in this group (crude and stored tobacco-seed oil) the levels of phospholipid and total cholesterol rose only very slightly or actually *fell* The level of free cholesterol consistently fell, but both the phospholipid and the free-cholesterol/esterified-cholesterol ratios were variable.

These different lipid responses were not associated with differences in the amounts of glyceride increase

In control experiments a fat-free diet, taken for 24 hours, reduced the levels of all the plasma lipids estimated.

Reproducibility of Lipid Response

Fig 3 shows the changes in cholesterol and phospholipid levels obtained with oils of the three groups Each volunteer received one oil four times, and on each occasion it produced the same kind of response, distinct from the effects of the other oils In the experiment recorded in fig 4, each of four volunteers took three different oils All four subjects showed the same type of lipid response to a given oil, and similar alterations in response when the oils were changed. (In fig 4, for simplicity, only the cholesterol changes are shown.)

Thus healthy people gave the same lipid response to a particular type of oil, even when the tests were separated

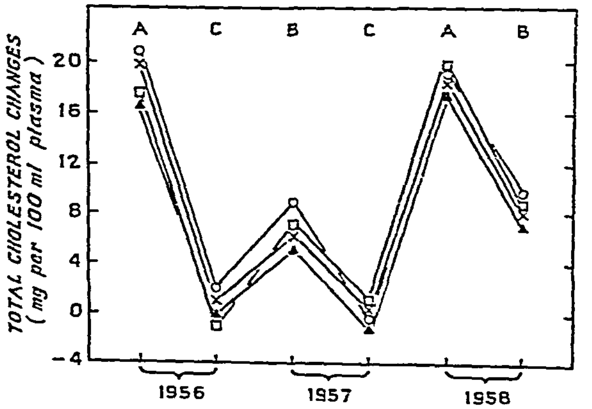

Fig 4—The “ swing ” of response in four subjects to three different types of oil (A, arachis B heated tobacco-seed oil C, crude tobacco-seed oil)

The fasting levels of total cholesterol in the four subjects were X, 181 mg per 100 ml, □, 211 mg ○ 183 mg, ▲, 189 mg by a year, and, by changing the oil, the volunteers could be " swung " to another response Clearly, the reproducibility of the results was not due to insensitiveness of the test This could in fact distinguish between the effects not only of different oils but even of the same oil before and after treatment by heat (table and fig 2)

Discussion

As a method of biological assay, the test feed has the advantage of simplicity, speed, and ease of control, and it enables us to ascertain the effects of single substances, using comparatively little material Their effects on plasma lipids are demonstrated not only (as in the longer experiments) by the changes in cholesterol and phospholipid but also by the relation of these lipids to one another and the relation of free cholesterol to esterified cholesterol The alterations in these relations are new findings which suggest that plasma-phospholipid and plasma-cholesterol levels are under separate physiological control Even in normal people the phospholipid/cholesterol ratio is not necessarily constant, and its different behaviour in response to group-1 and group-2 oils raises the interesting question whether it is ordinarily set by the diet

The different effects of crude and heated tobacco-seed oils is a further new finding, which will be discussed elsewhere The difference does not seem to be due to alterations in the fatty-acid composition of the oils

It is difficult to compare our results with those of other workers who have used single feeds for studying changes in the plasma lipids (Man and Gildea 1932, Lindholm 1956, Dole et al 1959), for, although Man and Gildea, for example, recorded similar phospholipid changes, their aim was to see whether lipid changes did in fact occur, and not to create a standard method of biological assay (Kingsbury 1958) Reasons why our findings may differ from those of the longer (more usual) experiments are numerous

1 The oils may have been subjected to different treatment (compare our different results with crude and heated tobacco-seed oils)

2 Most of the other work has been done on patients, whereas ours was on normal subjects

3 The results reported here concern only the period of lipid increase *immediately following the fatty meals*, whereas the results of long-term experiments must be the algebraic sum of varying lipid absorption, plasma-lipid increases, and clearance of lipids from the blood

4 The two methods may be sensitive to different variables

5 Whereas our results describe changes from a standard basal condition, the changes in the long-term experiments result from altering one diet for another This point can be illustrated by the fact that in the long experiments corn oil has so often caused an immediate and progressive *fall* in the plasma-cholesterol level, whereas in our experiments it caused a rise

It is all the more interesting, therefore, that our results should in many ways resemble those of Ahrens (1957), using the longer method In both investigations oils having iodine values above 100 produced low levels of plasma cholesterol, whereas with oils which have iodine values below 90 the cholesterol level increased with the saturation of the fat (see table) Whale, pilchard, and cod-liver-oil—which are rich in polyunsaturated acids but not in those essential for the normal health of animals (Thomasson 1953)—gave the same kinds of lipid responses as the edible vegetable oils (corn, soya, sunflower) whose high content of unsaturated acids is composed mainly of " essential " fatty acids This is similar to the results of Ahrens (1959)

In view of the similar effect of fish oils and vegetable oils on the plasma-cholesterol, it is interesting to reflect that, though an increase of tri-unsaturated acids in the tissue lipids of animals is strong evidence for a deficiency of the essential fatty acids (Jorgensen and Holman 1958), this accumulation of trienes has been reversed by cod-liver oil (Rieckenhoff et al 1949, Dam et al 1959), and that though this oil is rich in polyunsaturated acids, it has a very low essential-fatty-acid activity when assessed conventionally in terms of a normal skin in animals Thus it seems that many of the polyunsaturated acids, such as those found in cod-liver oil, may not only lower the blood-cholesterol level but also correct fatty-acid deficiencies

As conventionally defined, a " non-essential " acid very similar in physical properties to the " essential " linoleic acid is its *cis-trans* isomer, which has a melting-point of about −3°C (Privett et al 1955) or up to 7°C (Jackson et al 1952) Unfortunately it cannot yet be made in quantities sufficient for feeding experiments, but, as an alternative, we hoped to obtain low-melting-point isomers of linoleic acid from dehydrated ricinoleic acids (Hilditch 1956) Ultraviolet spectroscopic analysis (Hilditch et al 1951) of our fractions A and B showed that about 60% were linoleic acid or its isomers, of which about half were conjugated, probably the *cis-trans* isomers were concentrated in fraction B (melting-point 0–10°C) As both these fractions raised the plasma lipids only slightly (see table) it appeared that the lipid response to the natural *cis-cis* linoleic acid (approximately 70% of tobacco-seed oil) was neither prevented nor obscured by its conjugated or other isomers

Our results with tung oil are not at present explainable Sinclair (1959) has suggested that it should have the same effects as other non-essential oils of equal unsaturation, but this ignores its undoubtedly different properties, as evident in its chemical reactivity, rate of oxidation, and absorption spectra in the ultraviolet Possibly the biological action of conjugated fatty acids of this type differs from that of non-conjugated acids of equal unsaturation

The reasons for the different effects of the various oils are not yet established, but we cannot see why many factors in oils should not act in different ways For instance, the amount of the biologically essential linoleic acid usually given as a dietary supplement is about 50 g a day (Olson et al 1958) This would be about 5–10% of the total dry weight of the daily diet of our volunteers and probably about 10% of a patient's hospital diet In animals, however, severe essential-fatty-acid deficiency can be corrected by less than 0 5% of linoleic or arachidonic acid in the diet (Holman 1950)—an amount of arachidonic acid which is said to have no effect on the plasma lipids of man (Keys et al 1959) It may be that, in large amounts, unsaturated acids (both essential and non-essential) alter the physicochemical properties and hence the metabolism of their esters (glycerides, cholesterols, phospholipids, &c) (Klein and Martin 1959) This need not exclude a simultaneous correction of any existing fatty-acid deficiency (Fulco and Mead 1959)

In addition, an effect from the non-saponifiable or trace components of an oil cannot be excluded, and this may be the reason why crude tobacco-seed oil and heated tobacco-seed oil (though we have found no difference in their fatty-acid composition) have different effects

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In addition, an effect from the non-saponifiable or trace components of an oil cannot be excluded, and this may

Summary and Conclusions

A method for the biological assay of dietary lipids is described in which changes in the plasma glycerides, cholesterol, and phospholipids are measured after single 50 g. feeds of the fat under investigation. Plasma samples are collected before and 1½, 3½, 5½, 7–9, and 24 hours after the test feed.

The conditions for success are a period of fat deprivation and a clear fasting plasma before the experiment, a standard method of feeding, the avoidance of nausea, and adequate absorption of the oil. The criterion of adequate absorption is a rise in plasma glycerides by more than 60 mg. at 3½ hours, of which increase over a third must have been removed by 5½ hours.

The plasma-cholesterol and plasma-phospholipid changes produced by the feeds are called the lipid response. This response differs with different oils, the characteristic changes being reproducible both in different subjects and in the same subjects after long intervals.

The method has the advantage of needing only small amounts of material, of being quick and sensitive, of easily allowing experimental controls, and of not requiring special diets.

It is not offered as an alternative to long-term experiment, but as a supplementary method especially useful for rapid biological assays.

New contributions by this method are (1) the finding that different oils have different effects on the plasma phospholipid cholesterol ratios, (2) the use of these changing ratios to classify the type of lipid response to the experimental fat, and (3) the different effects of crude and heated oils.

The reasons for the different effects of the various oils are not known, but they are unlikely to be all due to one type of substance or property.

We wish to thank the volunteers, without whom the work would have been impossible and who received no recompense for much unpleasantness, Mr W Dorrel and Mr P A Dupont for technical assistance, Prof. C G Roo and Mr R W Best (Unilever Ltd.) for advice and interest, and Bush & Co for generous gifts of flavourings. Part of this work was included by K. J. K. in a thesis for the degree of doctor of philosophy, London University, 1958

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MYOCARDIAL INFARCTION AMONG MEMBERS OF COMMUNAL SETTLEMENTS IN ISRAEL

DANIEL BRUNNER
M.D. Vienna

GIDEON MANELIS
M.D. Geneva

From the First Medical Department and Research Laboratory for Degenerative Cardiovascular Diseases, Government Hospital, Jaffa, Israel

THE incidence of ischæmic heart-disease differs strikingly between different countries (World Health Organisation 1956) and even in a single country between different ethnic and social groups (Brock and Bronte Stewart 1955, Brunner and Löbl 1957, 1958, Dreyfuss 1953, Toor et al. 1957).

We have sought to examine the influence of physical exercise on the incidence of myocardial infarction in the Kibbutzim and Kvutzoth. These are communal settlements in Israel, whose members are ethnically homogeneous and where the environmental conditions (standard of living, diet, housing, cultural activity, and recreation) are virtually uniform. No difference is made between teachers, clerks, businessmen, local political leaders, drivers, fishermen, masons, and agricultural workers.

Material and Methods

This survey covers the incidence of myocardial infarction in the ten years up to Dec. 31, 1959, in 8500 people (4500 men and 4000 women) who at the end of 1949 were aged 30–55.

One of us (G. M.) visited each of the 58 settlements in which these people lived. Because of the comprehensive medical service in these settlements, we had no difficulty in obtaining data on all fatal cases (sickness certificates, hospital case-records, postmortem reports, and electrocardiograms) and surviving patients who had had myocardial infarcts (detailed clinical examination and electrocardiograms). All patients except 2 were admitted to hospital soon after the infarction. Thus the diagnosis of myocardial infarction, whether the patient survived or died, was based on the clinical picture and on an unequivocal electrocardiographical diagnosis. As electrocardiographic proof of myocardial infarction we accepted only typical Q waves or typical T waves, or both together. Not included in this review are patients who presented the clinical picture of angina pectoris with or without the electrocardiographic pattern of coronary insufficiency.

Findings

In the ten-year period there occurred, among the population of 8500, 111 cases of myocardial infarction, 34 patients died and 77 survived. Of the 4000 women, only 9 had infarction, and of these 2 died and 7 survived.

In the communal settlements of all persons in the age-group of the sample, 30% are engaged in sedentary work and 70% in non-sedentary work. By contrast, in the cases of myocardial infarction, of the 34 who died 19 were engaged in sedentary work, and, of the 77 who survived, 42 were engaged in sedentary work. The group of non-sedentary workers included also those doing very light bodily work, such as that of confectioner or light physical work in industrial factories. When classifying the men according to their occupation, we took into account work done by the patient for at least four years before the attack. Particular care was taken not to include in this or any other group men who had changed their occupation as a result of their illness.

For non-sedentary male workers the annual incidence was 1·36 per 1000, whereas for sedentary male workers the annual incidence was 4·1 per 1000. Thus the incidence was three times greater in the sedentary workers. The

mortality-rate was likewise three times greater in this group

Comment

These data support those of Morris (Morris et al 1953, Morris and Crawford 1958) indicating the preventive influence of bodily activity

Jewish people are reputedly especially prone to ischaemic heart-disease (Epstein et al 1957), but our findings do not support this belief The annual incidence of myocardial infarction among the sedentary Jewish workers whom we studied is almost identical with that in London sedentary workers observed by Morris et al (1953) On the other hand, the incidence of myocardial infarction among non-sedentary workers in Kibbutz (0 8 per 1000 men per year) is only half the incidence among London postmen who walked in their daily work (1 6 per 1000 men per year)

These findings underline the importance of physical exercise as a factor in the prevention of myocardial infarction

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INVOLUTIONARY SCLEROSIS AND DIASTOLIC HYPERTENSION

EFFECT OF ENVIRONMENTAL CHANGE

A M Cohen
M D Amer Univ Beirut
LECTURER IN MEDICINE

E Neumann
M D Lausanne
INSTRUCTOR IN OPHTHALMOLOGY

I C Michaelson
Ph D Glasg , F R F P S , D O M S
PROFESSOR OF OPHTHALMOLOGY

From the Department of Internal Medicine B, and Department of Ophthalmology, Rothschild Hadassah University Hospital, Jerusalem, Israel

Indirect evidence, based on hospital statistics, has shown that arteriosclerotic cardiovascular disease is more common among the Yemenite community who have lived in Israel for a long time than among new immigrants from Yemen (Dreyfuss 1953, Toor et al 1960) The blood-cholesterol and blood-phospholipids are higher among Yemenites settled in Israel than among new immigrants from Yemen (Toor et al 1954, Brunner et al 1955) It was shown by one of us that there is practically no diabetes mellitus among new immigrants from Yemen, while among those settled in Israel for more than twenty-five years, its prevalence is comparable to that among Jews from the western world (Cohen 1960)

The purpose of our investigation was to determine whether the difference in environment between Yemen and Israel also affects the prevalence of involutionary sclerosis and diastolic hypertension among these contrasting groups Yemenite Jews form particularly suitable material for this study, being a homogeneous group with little or no intermarriage with other groups Constitutional factors, therefore, cannot affect the clinical differences between the settled and the new immigrant groups

In order to have the groups unselected, the entire Yemenite population above the age of 30 in chosen areas were visited in their homes The diagnosis of diastolic hypertension was based on manometric examination, and that of involutionary sclerosis on ophthalmoscopic examination of the retinal vessels This procedure seems to be as reliable as any one method for the diagnosis of involutionary sclerosis, and is probably the most suitable for a house-to-house examination It is, however, appreciated that changes in the retinal blood-vessels do not necessarily indicate changes in the entire vascular tree, nor does the absence of any change rule out the possibility of arteriosclerosis in other parts of the body

Material and Methods

The survey was carried out during 1959 The first group, the " new immigrants ", consisted of the entire population, over the age of 30, in two settlements near Jerusalem, Yishi and Noham They had all immigrated from the Yemen within the past ten years The group contained 147 persons, 70 men and 77 women The second, the " settled " group, consisted of the entire population, over the age of 30, in two Jerusalem quarters, Nahalat Ahim and Mishkenot They all had lived in Israel for over twenty-five years, and some were born there This group contained 125 persons, 55 men and 70 women All examinations were carried out at their homes Age, sex, and time of arrival to this country were noted A short physical examination was carried out in each case Resting blood-pressure was taken several times Urine was examined for albumin with sulphosalicylic acid, and for glucose with glucose reductase (' Test Tape ', Lilly)

Diastolic hypertension was considered to be present when the systolic pressure exceeded 140–150 mm Hg, and the diastolic 90 mm Hg The criteria for involutionary sclerosis were (*a*) narrow retinal arteries, (*b*) unusually straight course of these vessels, and (*c*) narrowness of their bifurcations Many of these cases showed slight variations in calibre of the arteries, and some changes at the arteriovenous crossings These were not, however, thought to be essential for the diagnosis of involutionary sclerosis The arteries were considered to

TABLE I—AGE (YEARS) AND SEX-DISTRIBUTION IN THE TWO GROUPS

—	30–55 years				Over 55 years				Total	
	M		F		M		F		M	F
	Number of patients	Average age	Number of patients	Average age	Number of patients	Average age	Number of patients	Average age		
New	44	40 0 ± 7 8*	59	41 5 ± 7 3	26	69 2 ± 7 0	18	67 1 ± 8 0	70	77
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Table I shows the average age in each age-group for men nd women is almost the same in the " settled " and " new mmigrants " groups

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TABLE II—PREVALENCE (AS A PERCENTAGE) OF DIASTOLIC HYPERTENSION IN THE TWO GROUPS

—	30–55 years	Over 55 years
New	1% (0 M, 2 F)	7% (4 M 11 F)
Settled	7 5% (7 M 8 F)	20% (20 M, 21 F)
P	0 03	0 04

Proteinuria was found once in the 4 hypertensives among the new immigrants, and five times in the 17 hypertensives among settled Yemenites

It is of interest that, though there were no diabetics among the new immigrants, there were 9 among the settled group (6 men and 3 women), 8 being more than 60 years old

The percentage of cases with involutionary sclerosis, but without diastolic hypertension or diabetes, among the new immigrants and old settlers is given in table III

TABLE III—PREVALENCE (AS A PERCENTAGE) OF RETINAL INVOLUTIONARY SCLEROSIS IN THE TWO GROUPS

—	30–55 years			Over 55 years		
	Total	M	F	Total	M	F
New	3%	0	5	8%	9	6
Settled	18 %	7	27	34%	26	33
P		0 16	0 002		0 006	

There was a statistically significant difference in the prevalence of involutionary sclerosis between the " new " and " settled " in the age-group 55+ and between " settled " and " new " women in the age-group 30–55 No significant difference was found in the men of the age-group 30–55

Discussion

It can be seen that there is a greater prevalence of diastolic hypertension, and of the ageing process as seen in the retina, among the Yemenites who have lived in Israel for over 25 years as compared with Yemenite new immigrants who have not lived for more than 10 years in the country The findings parallel the differences in the prevalence of diabetes, and in the blood-cholesterol and blood-phospholipids estimates between both groups and confirm the impression that cardiovascular disease and arteriosclerosis are more prevalent in the settled group

There is a great difference between the conditions of life in Israel and in Yemen, and there is little doubt that the different prevalences of hypertension and involutionary sclerosis between the two groups is the result of these differences The lack of intermarriage with other groups of Jews eliminates constitutional and genetic factors as an explanation of the differences The main differences between the two groups are in food habits and in the general strain of living to which they are exposed The latter can be best described as the ambition for a higher standard of living, and the general " speeding-up " involved in the Western style of culture

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RADIOLOGICAL LUNG-FUNCTION STUDIES

R E Steiner
M D N U I , M R C P , F F R
DIRECTOR, DEPARTMENT OF RADIODIAGNOSIS

J W Laws
M B Sheff, M R C P , F F R
HONORARY LECTURER IN RADIODIAGNOSIS

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M J McDonnell
SENIOR
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DEPARTMENT OF BIOPHYSICS
HAMMERSMITH HOSPITAL AND POSTGRADUATE MEDICAL SCHOOL OF LONDON, LONDON, W 12

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Attempts have been made by Kjellberg et al (1950) to study variations in pulmonary blood-flow by recording lung-density variations, using an electrokymographic method described by Engstrom et al (1949) Marchal et al (1946, 1949, 1959) have studied lung-density variation during respiration, paying particular attention to the pulsation of the pulmonary arteries These authors have also found that the variation in density of each lung during respiration correlates well with bronchospirometric findings Other workers (Simonin et al 1950, 1951) have attempted to study lung function by photometric comparison of the film densities on inspiration and expiration of similar areas of lung, radiographed through a kymographic grid They have compared this method with electrokymographic measurements of lung density, and compared both methods with bronchospirometry

Methods

Description of Apparatus

The apparatus is illustrated in figs 1a and b

The image of the lung field, formed on the phosphor of a 5-in Philips image-intensifier, is viewed through a binocular eyepiece to establish the exact area under examination A photomultiplier (R C A type 913) in a special mounting is substituted for the eyepiece An iris diaphragm is fitted to the

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patient Fig 1 illustrates our technique, using a dialyser with 18 m of cellophane tubing

The perforated metal cylinders which form the screens for the cellophane spiral must be reinforced by a metal " skeleton " The inner cylinder would otherwise be damaged during operation by the considerable pressure resulting from application of positive pressure over a large surface Blood is pumped from the patient by a ' Sigma ' finger pump with adjustable speed (fig 1, P) The pump can be adjusted to ' occlusive " setting, which makes the rate of blood-flow relatively independent of the pressure head in A A is a simple manometer system which records the blood-pressure before it enters the proximal cellophane coils S is the cellophane spiral where ultrafiltration takes place This spiral is immersed in bath fluid B is a manometer system which records the blood-pressure as it leaves the distal coils The outflow tube can be narrowed by an adjustable screw, K, whereupon the pressure in B and in A will increase By using manometers A and B various pressure-flow relations can be recorded, this system also allows the blood flow-rate to be measured in vitro

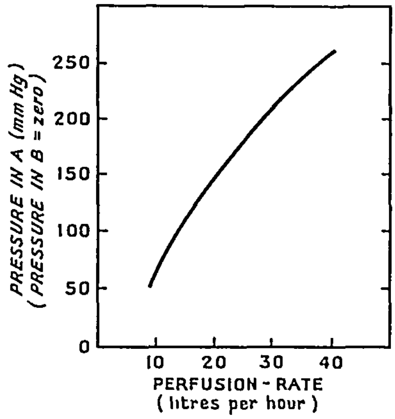

Fig 2—Pressure-flow relations in ultrafiltration with an 18 m cellophane tube, and without constriction of outflow tube
The pressure in A reaches 200 mm Hg at a perfusion-rate of 30 litres per hour

Fig 2 shows the increase in pressure in A when the rate of flow is increased without raising the pressure in B by creating a resistance at K As maximum safe pressure we have empirically chosen 200 mm Hg Above this pressure the inner cylinder may be damaged (even when reinforced) or the cellophane tube may leak 200 mm Hg pressure in A is achieved with a flow-rate of 30 litres per hour

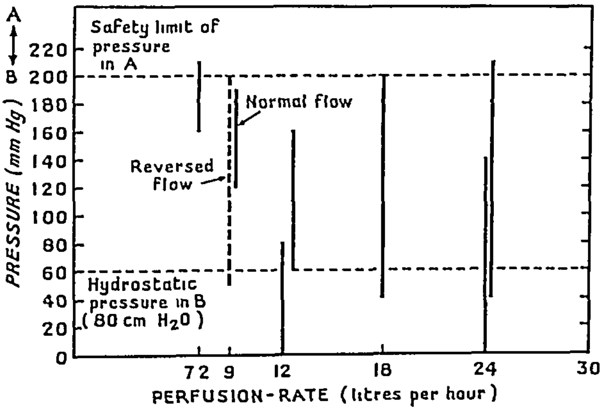

Fig 3—Pressure-flow relations with an 18 m cellophane ultrafiltrator
Pressure at B is variably increased Only moderate perfusion rates allow the pressure at B to increase considerably without excessive increase at A

Fig 3 shows the pressure-flow relations if the resistance at R is increased Each vertical column represents at the top the pressure in A, and at the bottom the pressure in B, at a certain flow-rate High flow-rates do not permit high pressures in B, because the pressure in A would then pass the safety limit Ultrafiltration will be most efficient, however, if it takes place along the whole length of the cellophane tubing, and for this a high pressure is necessary in B This can only be obtained with a moderate perfusion-rate Too low a rate is unfavourable because the blood becomes excessively dehydrated, and ultra filtration is handicapped by increasing colloid-osmotic pressure A moderate flow of 10–12 litres per hour seems to be best for ultrafiltration If the direction of blood-flow is reversed (from below upwards) the pressure difference between A and B increases considerably because the hydrostatic pressure of the bath fluid has now to be overcome at A The resulting mean pressure $\frac{(A+B)}{2}$ is lower than with a normal flow, hence the direction of the blood-stream should be downwards

The efficiency of dialysis is greater if the flow-rate is increased (fig 4) High perfusion-rates (20–30 litres per hour) result in rapid clearances and consequently short dialyses If dialysis is combined with ultrafiltration, however, moderate flows of 10–12 litres per hour seem preferable

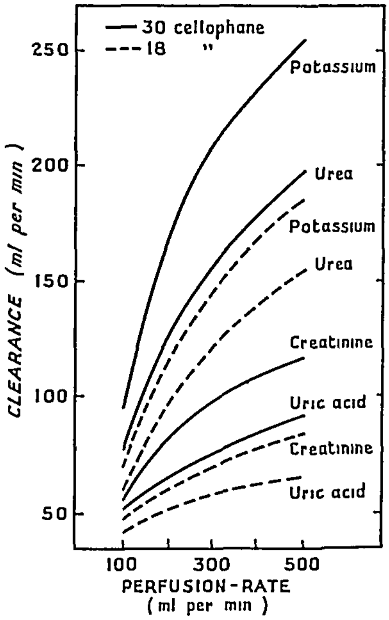

Fig 4—In-vitro clearances of the Alwall kidney at different perfusion-rates

We observed in vitro a water extraction of about 300 ml per hour—a figure which correlates well with our clinical experience and with other published data Higher rates of dehydration may lead to shock and hypotension The above rate was well tolerated by overhydrated patients, and it did not cause hypotension, although hypertension was sometimes reduced to normal

Summary

The artificial kidney of the Alwall type can be used for controlled ultrafiltration by creating a pressure difference between the extracorporeally circulating blood and the bath fluid

The optimal flow-rate for ultrafiltration is lower than that for dialysis

In clinical ultrafiltration water extraction of 300 ml per hour did not lead to hypotension if the patient was overhydrated

STAPHYLOCOCCAL PNEUMONIA IN THE NEONATAL PERIOD

R L Edwards
M B Lond , M R C O G
ELMORE STUDENT, UNIVERSITY OF CAMBRIDGE

G A Gresham
M A , M D Cantab
UNIVERSITY LECTURER IN PATHOLOGY

THE DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAMBRIDGE

The pattern of tissue reaction to microbial infection varies with the virulence of the organism, the resistance of the host, and occasionally with the portal by which the organism gains access Neonatal lung infection with the staphylococcus illustrates this point

We describe here eight examples of staphylococcal pneumonia in the neonate which occurred during the period March, 1958, to August, 1959 They illustrate the often fulminant character of the infection and the variety of histological appearances in the lungs, and emphasise the need for the diligent use of the aseptic method in the care of the newly born

Illustrative Case-record

Stillborn infant, aged 39 weeks The mother, a multipara aged 31, was admitted with toxæmia on Aug 5, 1959, at 37th week of pregnancy She was kept in bed, but her hypertension did not lessen and it was decided to induce labour by hind-water rupture of the membranes, this was done on Aug 14 The next day an oxytocin (' Pitocin ') drip was given which induced uterine contractions

The temperature rose to 105°F on the following day, with a rigor, tenderness was noted in the right loin and right iliac fossa A diagnosis of pyelitis of pregnancy was made, urine examination showed a few pus cells, and *Proteus vulgaris* was cultured A high vaginal swab produced a growth of *Staphylococcus pyogenes*, sensitive to most antibiotics, the organism was not present in the patient's nose Benzyl penicillin (penicillin G) 500,000 units and streptomycin 0 5 g were given twice daily On the same day, when the cervix was two finger breadths dilated, at approximately 1 30 P M , the fœtal heart sounds became inaudible

She was delivered at 3 45 P M on Aug 16 of a stillborn male fœtus weighing $5^1/_4$ lb (2410 g) Her temperature became normal next day, and recovery was uneventful

Necropsy

Tiny hæmorrhages were scattered over the visceral pleuræ of both lungs and over the visceral pericardium Small quantities of blood-stained fluid were seen in both pleural and pericardial cavities The spleen weighed 14 g , and appeared normal

No other abnormality was found The placenta and umbilical cord appeared normal macroscopically

Histological Findings

Lungs —All lobes of the lungs contained areas of intra-alveolar hæmorrhage, mingled with clusters of polymorphonuclear leucocytes and clumps of staphylococci There were numerous epithelial squames in alveoli and alveolar ducts A few veins contained thrombi

Placenta —Areas of purulent infiltration were seen in sections of placenta and umbilical cord

Bacteriological Investigations

The lungs and spleen were examined by the method described by Gresham and Gleeson-White (1957) All lobes grew a strain of *Staph pyogenes*, sensitive to all antibiotics against which it was tested (case 8, table III) The spleen was sterile

The findings in the other cases in this series are summarised in table I

Discussion

All infants showed histological evidence of pneumonia which varied from predominantly hæmorrhagic to frankly purulent infiltration In every case *Staph pyogenes* was isolated from the lungs

The histological appearances in the lungs could be classified broadly into three main groups

1 Extensive intra-alveolar hæmorrhage with necrosis of alveolar walls, together with abundant staphylococci Polymorphonuclear leucocytic infiltration was scanty This appears to represent an overwhelming infection—the organism being at the peak of its virulence and the host resistance low Two cases (1 and 6) fall into this group

2 Five showed the usual appearances of bacterial bronchopneumonia with sparse intrapulmonary hæmorrhage The duration of illness in these cases (3–7) was of the order of days rather than hours, as in the first group

3 One showed sparse polymorphonuclear leucocytic infiltration in alveoli (case 2) The staphylococcus was isolated both from the lung and from the spleen The changes in the lungs reflected those seen in other organs and were due to septicæmia

Five cases were infected with *Staph pyogenes* of the same antibiotic resistance patterns as those of the indigenous hospital staphylococcus This suggested that the source of infection was the hospital environment The route of infection in at least four of these was probably vaginal, three showed placentitis on histological examination In one (case 7) the infant was delivered at another hospital and the placenta was not available Nevertheless, the mother's vagina contained a *Staph pyogenes* similar in antibiotic resistance pattern to that isolated from the fœtal lung The finding of placentitis strongly supports the view that the bronchopneumonia in the fœtus was due to inhalation of infected amniotic fluid Further evidence

TABLE I—CLINICAL FEATURES

Case no	Antenatal history	Duration of pregnancy in weeks	Delivery	Stillbirth or neonatal death	History of infant	Duration of life
1	Essential hypertension toxæmia P.R.M	31	Normal	N N.D	Neonatal asphyxia intragastric oxygen	42 hours
2	5 threatened abortions P.R.M	30	Normal fœtal distress	N N.D	Neonatal asphyxia intragastric oxygen	37 hours
3	2 false labours	42	Normal fœtal distress	N.N.D	Neonatal asphyxia intragastric oxygen	4 days
4	Emergency admission at full dilatation	36	Normal	N N D	Not intubated	11 days
5	Toxæmia P.R M	38	Normal	N.N D	Not intubated	18 days
6	Eclampsia P R.M	33	Cæsarean section	N N.D	Not intubated oxygen by positive-pressure mask	36 hours
8	Toxæmia A R.M	39	Oxytocin drip rigors during labour temp 105 F fœtal distress N D	S.B	Not available	Not known

P.R.M =premature rupture of membranes A.R.M =artificial rupture of membranes S.B =stillbirth N.N D =neonatal death N.D =normal delivery

Analysis of the density curves is concerned with (1) the amplitude of the density variation in relation to the spirometer tracings, and (2) alterations in the time relationship between the two tracings

To illustrate these points two examples are described

Case 1 *Pulmonary emphysema with bullous emphysema of the right lower zone*—The spirometer tracings were similar during the examination of each of the four areas Normal respiration with a tidal flow of 1000–1200 ml of air was followed by a full inspiration (held for approximately 5 sec) and finally the forced expiration of approximately 2000 ml of air The forced expiration was considerably slower than in the normal subject (fig 6)

In the areas examined, the density tracings show considerable differences in amplitude and timing The left lower-zone tracing appears almost normal, following the spirometer curve closely The curve is synchronous with the spirometer tracing and the only abnormality is that, on forced expiration, the rate of loss of density is less than in the normal In the left upper-zone tracings, on forced expiration, there is a rapid initial loss of density, followed by a sudden check, and then a more gradual loss of density This contrasts with the smooth curve obtained from the lower zone The density tracing in the right upper zone is similar on forced expiration, but there is very little variation in lung density on normal respiration The density tracing in the right lower zone is grossly abnormal The density and spirometer curves are completely out of phase During respiration, the lung becomes more dense on inspiration and less dense on expiration On forced expiration, the lung initially becomes a little less dense and then shows no further change, even though the spirometer curve indicates that air is being expired from the lungs as a whole

Comment—The left lower zone is the area in which the tracings are nearest to normal There is the good synchronous variation in density with respiration, and an even loss of density on forced expiration This suggests that the most useful air movement is taking place in this area of the lung The upper zones, by comparison, show little variation in density on respiration On forced expiration, the sudden check in the density curve suggests that there is partial air-trapping after the start of expiration

The curves in the right lower zone are paradoxical, the density curve shows brightening on expiration The explanation for this is not known, but it may be due to air movement within the lungs, the air flowing into this region from other parts of the lungs

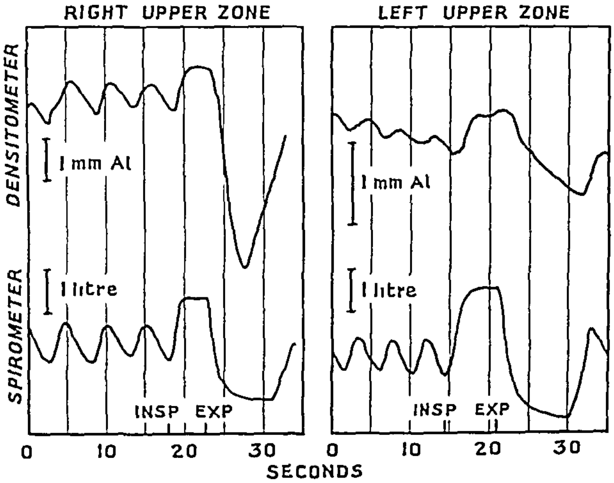

Fig 7—Case 2 Unilateral hypertranslucency of the left lung

The most important features are the smaller amplitude of density change on respiration and the slower rate of loss of density on forced expiration of the left upper zone compared with the right Since the densitometer sensitivity was greater when the left recording was made, the difference between the two sides is greater than appears at first sight

Case 2 *Radiological translucency of one lung*—A young man, without symptoms, was found, on routine X-ray examination, to have unilateral hypertranslucency of the left lung (Macleod 1954) The right pulmonary arteries appeared normal but the left pulmonary arteries appeared abnormally small Fluoroscopic examination showed that on expiration the left lung failed to deflate fully and the mediastinum swung to the right

The tracings obtained for the right and left upper zones are shown in fig 7 The spirometer tracings were similar when the two areas were examined The density and spirometer curves show synchronous movement But on normal respiration there is a much smaller amplitude of density change in the left upper zone when compared with the right On forced expiration, there is a much slower rate of loss of density in the left than in the right lung Similar changes were found in other zones It should be noted that the densitometer sensitivity was greater when recording the left side than when recording the right side (see scale fig 7), which means that the actual difference in density is greater than appears on the graphs

Comment—The small variation in lung density on normal respiration and the slow loss of density on forced expiration probably indicate that there is a much reduced air flow into and out of the left lung when compared with the right

Discussion

A number of factors, pulmonary and extrapulmonary, influence the overall radiolucency of the lung-fields during respiration The extrapulmonary factors are the ribs and soft tissues of the thoracic cage Their influence on the density curves is small On inspiration, the girth of the thoracic cage increases, thinning the overlying soft tissues and making them slightly more radiolucent This change is in phase with and slightly augments the overall pulmonary density curve The change in density caused by the ribs moving across the field during respiration is less regular than the soft-tissue effect By choosing a 5 cm diameter field, it is possible to even out the density changes produced by the ribs For example, the effect of the ribs and soft tissues over a pneumothorax, when no lung is in the field, is small compared with the changes in density over a normal lung field

The variation in radiolucency attributable to the pulmonary components are due to changes in blood contents and changes in air contents, the vascular component causes only a small ripple on the relatively large pulmonary density curve The main density changes are due to the air component

Sokolov (1956) has shown, by inflating the lungs of cadavers under experimental conditions, that the decrease in density which occurs with pulmonary inflation is dependent upon the total amount of lung tissue through which the X rays pass, and that this depends mainly on the amount of lung expansion which takes place in directions perpendicular to the rays Thus, in an anterior view of a lung, the decrease in density is influenced mainly by expansion in the vertical and transverse directions, in the coronal plane, and only little by expansion in the anteroposterior direction

The alterations of lung density during respiration, recorded by our densitometer, are a function of the degree of expansion of the part of lung under observation, and hence of the amount of air exchanged Since the observations are carried out under dynamic conditions, the curves give some indication of the air flow into and out of this part of the lung There is a recognisable normal pattern of tracings in different parts of the lung fields When there are abnormalities, correlation of the density tracings in the different areas with the spirometer tracings allows one to detect abnormalities of air flow When alterations in lung density occur without spirometer movement, intrapulmonary air flow must be taking place When there is localised air trapping, the densitometer tracing may show a slow rate of loss of density even though the spirometer tracings may be relatively normal Normally the densitometer and spirometer tracings are synchronous Asynchronous curves imply localised air-flow obstruction, or even reversal, as in one of our cases

The place of this radiological technique in the study of lung function has not yet been fully assessed It is hoped to correlate this method with other more conventional lung-function tests in order to establish its clinical value as a routine procedure

Summary

A radiological method of studying localised changes in lung density during respiration is described Simultaneous spirometer recordings are made

The curves obtained in normal and abnormal patients are described and analysed

The significance and interpretation of these findings is discussed

We wish to thank Mr C R. Brecknell for the figures, and Dr G C. Rivett for allowing us to carry out density studies on case 2

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OPTIMAL PERFUSION-RATE IN HÆMODIALYSIS COMBINED WITH ULTRAFILTRATION

E E Twiss
M.D Amsterdam

M M P Paulssen
Ph D Amsterdam

DIALYSIS DEPARTMENT, ST CLARA HOSPITAL, ROTTERDAM,
THE NETHERLANDS

In acute renal insufficiency patients not infrequently become overhydrated as water is liberated from the cells by catabolic processes Water is also formed by oxidation of body fat and dextrose To prevent overhydration the intake of water must be rigorously restricted (to 400–500 ml per day) during the anuric phase Overhydration may lead to pulmonary œdema and bronchopulmonary infection, and cerebral œdema sometimes causes convulsions, especially when too much sodium has been given in an attempt to correct acidosis

If progressive uræmia is complicated by severe overhydration, treatment with combined hæmodialysis and ultrafiltration is indicated Ultrafiltration occurs if the pressure in the extracorporeally circulating blood (i e, the colloid-osmotic pressure of the plasma) is at least 30 mm Hg higher than the pressure in the surrounding bath fluid, this is technically *feasible only if the filter* membrane (' Cellophane ') is supported by a rigid screen which prevents changes of the extracorporeal blood-volume Kolff's rotating kidney lacks this support, and therefore cannot be used as an ultrafiltrator Kolff's twin-coil kidney, however, is supported, in this type of kidney ultrafiltration is obligatory because the high inner resistance of the narrow cellophane coils demands a high perfusion pressure But the Skegg-Leonards and Alwall types of kidney seem preferable because they both give support to the cellophane membrane and allow controlled ultrafiltration

Method

In our department a modified Alwall dialyser has been used since 1952 Under standard conditions the patient loses no water As the inner resistance of the cellophane tubing spiral is low, a moderate perfusion pressure suffices for satisfactory flow This slight " over " pressure is partially compensated by the colloid-osmotic pressure and partially by the hydrostatic pressure of the bath fluid If the direction of flow through the cellophane spiral is from above downwards, the proximal coils will cause some ultrafiltration because the blood-pressure is high and the hydrostatic pressure of the bath fluid is low The distal coils will take up water from the bath because the perfusion pressure is low and the hydrostatic pressure of the bath is high In practice this maintains the water balance, as is shown by weighing the patient with a bed scale before, during, and after dialysis The bath fluid we use is not hypertonic to uræmic plasma

Ultrafiltration is made possible by placing an airtight lid on the bath-fluid reservoir, so creating a negative pressure in the air above the bath fluid The hydrostatic pressure in the bath will thus be lowered, and a pressure gradient will be established between bath fluid and blood This method has several disadvantages, including the high cost of airtight apparatus, the maintenance of a constant vacuum, and the sudden changes in blood-volume which arise during the rapid creation of a vacuum (although these changes are limited by the screen support, they may disturb the patient) A much simpler, cheaper, and easier way is to raise the pressure of the circulating blood This can be done by using a higher perfusion-rate, and by increasing the resistance in the circuit by constricting the outflow tube from the " kidney " to the

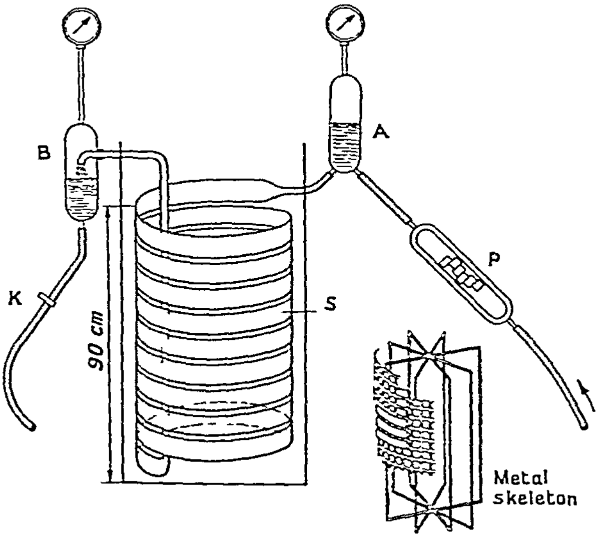

Fig 1—Schematic drawing of the Alwall kidney as ultrafiltrator
P=finger pump A and B=manometers respectively proximal and distal to the cellophane spiral, S K=adjustable screw

patient Fig 1 illustrates our technique, using a dialyser with 18 m of cellophane tubing

The perforated metal cylinders which form the screens for the cellophane spiral must be reinforced by a metal " skeleton " The inner cylinder would otherwise be damaged during operation by the considerable pressure resulting from application of positive pressure over a large surface Blood is pumped from the patient by a ' Sigma ' finger pump with adjustable speed (fig 1, P) The pump can be adjusted to ' occlusive " setting, which makes the rate of blood-flow relatively independent of the pressure head in A A is a simple manometer system which records the blood-pressure before it enters the proximal cellophane coils S is the cellophane spiral where ultrafiltration takes place This spiral is immersed in bath fluid B is a manometer system which records the blood-pressure as it leaves the distal coils The outflow tube can be narrowed by an adjustable screw, K, whereupon the pressure in B and in A will increase By using manometers A and B various pressure-flow relations can be recorded, this system also allows the blood flow-rate to be measured in vitro

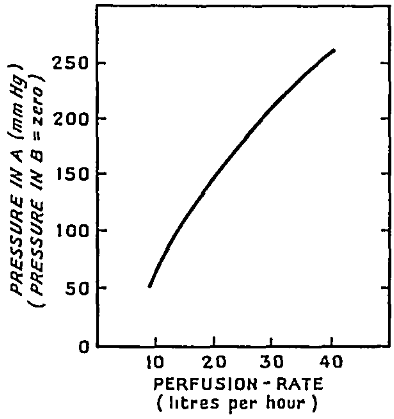

Fig 2—Pressure-flow relations in ultrafiltration with an 18 m cellophane tube, and without constriction of outflow tube

The pressure in A reaches 200 mm Hg at a perfusion-rate of 30 litres per hour

Fig 2 shows the increase in pressure in A when the rate of flow is increased without raising the pressure in B by creating a resistance at K As maximum safe pressure we have empirically chosen 200 mm Hg Above this pressure the inner cylinder may be damaged (even when reinforced) or the cellophane tube may leak 200 mm Hg pressure in A is achieved with a flow-rate of 30 litres per hour

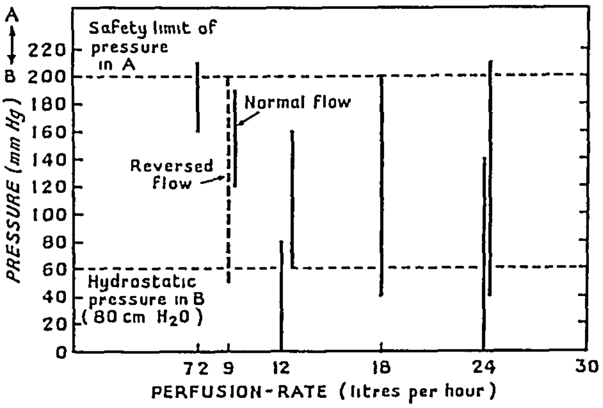

Fig 3—Pressure-flow relations with an 18 m cellophane ultrafiltrator

Pressure at B is variably increased Only moderate perfusion rates allow the pressure at B to increase considerably without excessive increase at A

Fig 3 shows the pressure-flow relations if the resistance at R is increased Each vertical column represents at the top the pressure in A, and at the bottom the pressure in B, at a certain flow-rate High flow-rates do not permit high pressures in B, because the pressure in A would then pass the safety limit Ultrafiltration will be most efficient, however, if it takes place along the whole length of the cellophane tubing, and for this a high pressure is necessary in B This can only be obtained with a moderate perfusion-rate Too low a rate is unfavourable because the blood becomes excessively dehydrated, and ultrafiltration is handicapped by increasing colloid-osmotic pressure A moderate flow of 10–12 litres per hour seems to be best for ultrafiltration If the direction of blood-flow is reversed (from below upwards) the pressure difference between A and B increases considerably because the hydrostatic pressure of the bath fluid has now to be overcome at A The resulting mean pressure $\frac{(A+B)}{2}$ is lower than with a normal flow, hence the direction of the blood-stream should be downwards

The efficiency of dialysis is greater if the flow-rate is increased (fig 4) High perfusion-rates (20–30 litres per hour) result in rapid clearances and consequently short dialyses If dialysis is combined with ultrafiltration, however, moderate flows of 10–12 litres per hour seem preferable

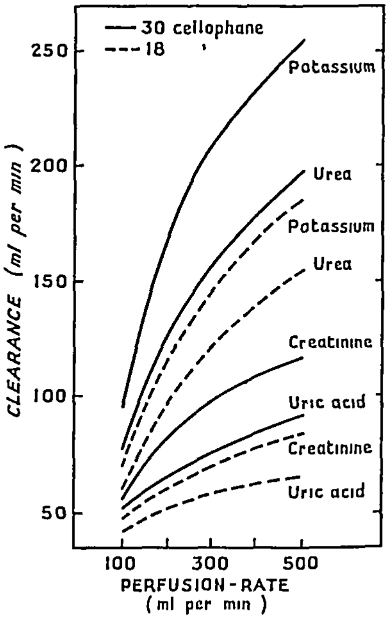

Fig 4—In-vitro clearances of the Alwall kidney at different perfusion-rates

We observed in vitro a water extraction of about 300 ml per hour—a figure which correlates well with our clinical experience and with other published data Higher rates of dehydration may lead to shock and hypotension The above rate was well tolerated by overhydrated patients, and it did not cause hypotension, although hypertension was sometimes reduced to normal

Summary

The artificial kidney of the Alwall type can be used for controlled ultrafiltration by creating a pressure difference between the extracorporeally circulating blood and the bath fluid

The optimal flow-rate for ultrafiltration is lower than that for dialysis

In clinical ultrafiltration water extraction of 300 ml per hour did not lead to hypotension if the patient was overhydrated

STAPHYLOCOCCAL PNEUMONIA IN THE NEONATAL PERIOD

R. L. Edwards
M.B. Lond., M.R.C.O.G.
ELMORE STUDENT, UNIVERSITY OF CAMBRIDGE

G. A. Gresham
M.A., M.D. Cantab
UNIVERSITY LECTURER IN PATHOLOGY

THE DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAMBRIDGE

The pattern of tissue reaction to microbial infection varies with the virulence of the organism, the resistance of the host, and occasionally with the portal by which the organism gains access. Neonatal lung infection with the staphylococcus illustrates this point.

We describe here eight examples of staphylococcal pneumonia in the neonate which occurred during the period March, 1958, to August, 1959. They illustrate the often fulminant character of the infection and the variety of histological appearances in the lungs, and emphasise the need for the diligent use of the aseptic method in the care of the newly born.

Illustrative Case-record

Stillborn infant, aged 39 weeks. The mother, a multipara aged 31, was admitted with toxæmia on Aug. 5, 1959, at 37th week of pregnancy. She was kept in bed, but her hypertension did not lessen and it was decided to induce labour by hind-water rupture of the membranes; this was done on Aug. 14. The next day an oxytocin ('Pitocin') drip was given which induced uterine contractions.

The temperature rose to 105°F on the following day, with a rigor; tenderness was noted in the right loin and right iliac fossa. A diagnosis of pyelitis of pregnancy was made; urine examination showed a few pus cells, and *Proteus vulgaris* was cultured. A high vaginal swab produced a growth of *Staphylococcus pyogenes*, sensitive to most antibiotics; the organism was not present in the patient's nose. Benzyl penicillin (penicillin G) 500,000 units and streptomycin 0.5 g. were given twice daily. On the same day, when the cervix was two finger breadths dilated, at approximately 1.30 P.M., the fœtal heart sounds became inaudible.

She was delivered at 3.45 P.M. on Aug. 16 of a stillborn male fœtus weighing 5¹/₄ lb. (2410 g.). Her temperature became normal next day, and recovery was uneventful.

Necropsy

Tiny hæmorrhages were scattered over the visceral pleuræ of both lungs and over the visceral pericardium. Small quantities of blood-stained fluid were seen in both pleural and pericardial cavities. The spleen weighed 14 g., and appeared normal.

No other abnormality was found. The placenta and umbilical cord appeared normal macroscopically.

Histological Findings

Lungs.—All lobes of the lungs contained areas of intra-alveolar hæmorrhage, mingled with clusters of polymorphonuclear leucocytes and clumps of staphylococci. There were numerous epithelial squames in alveoli and alveolar ducts. A few veins contained thrombi.

Placenta.—Areas of purulent infiltration were seen in sections of placenta and umbilical cord.

Bacteriological Investigations

The lungs and spleen were examined by the method described by Gresham and Gleeson-White (1957). All lobes grew a strain of *Staph. pyogenes*, sensitive to all antibiotics against which it was tested (case 8, table III). The spleen was sterile.

The findings in the other cases in this series are summarised in table I.

Discussion

All infants showed histological evidence of pneumonia which varied from predominantly hæmorrhagic to frankly purulent infiltration. In every case *Staph. pyogenes* was isolated from the lungs.

The histological appearances in the lungs could be classified broadly into three main groups:

1. Extensive intra-alveolar hæmorrhage with necrosis of alveolar walls, together with abundant staphylococci. Polymorphonuclear leucocytic infiltration was scanty. This appears to represent an overwhelming infection—the organism being at the peak of its virulence and the host resistance low. Two cases (1 and 6) fall into this group.

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Five cases were infected with *Staph. pyogenes* of the same antibiotic resistance patterns as those of the indigenous hospital staphylococcus. This suggested that the source of infection was the hospital environment. The route of infection in at least four of these was probably vaginal; three showed placentitis on histological examination. In one (case 7) the infant was delivered at another hospital and the placenta was not available. Nevertheless, the mother's vagina contained a *Staph. pyogenes* similar in antibiotic resistance pattern to that isolated from the fœtal lung. The finding of placentitis strongly supports the view that the bronchopneumonia in the fœtus was due to inhalation of infected amniotic fluid. Further evidence

TABLE I—CLINICAL FEATURES

Case no.	Antenatal history	Duration of pregnancy in weeks	Delivery	Stillbirth or neonatal death	History of infant	Duration of life
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4	Emergency admission at full dilatation	36	Normal	N.N.D.	Not intubated	11 days
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6	Eclampsia. P.R.M.	33	Cæsarean section	N.N.D.	Not intubated, oxygen by positive-pressure mask	36 hours
8	Toxæmia. A.R.M.	39	Oxytocin drip rigors during labour temp 105°F fœtal distress N.D.	S.B.	Not available	Not known

P.R.M. = premature rupture of membranes. A.R.M. = artificial rupture of membranes. S.B. = stillbirth. N.N.D. = neonatal death. N.D. = normal delivery.

TABLE II—PATHOLOGY

Case no	Weight (g)	Ossification centres	Lung	Œsophagus	Other organs	Placenta
1	1320	C	Lung hæmorrhage, pneumonia, squames ±	Œsophagitis	Normal	No inflammatory changes
2	955	C, Ta	Pneumonia, squames ++	Œsophagitis	Normal	Inflammatory reaction in placenta and cord
3	1397	C, Ta	Bronchopneumonia, squames ++	Œsophagitis	Normal	Inflammatory reaction in placenta and cord
4	2270	C, Ta, F	Bronchopneumonia, no squames	Normal	Meningitis, hydrocephalus, meningomyelocele, spina bifida, C D H	No infection
5	1620	C, Ta, F, Ti	Bronchopneumonia, no squames	Normal	Meningitis, pericarditis microcephaly, proptosis, spina bifida	Not available
6	1122	C, Ta	Lung hæmorrhage, broncho pneumonia, squames ±	Normal	Normal	No infection
7	1055	C, Ta	Bronchopneumonia, squames ++	Normal	Staphylococcal enteritis	Not available
8	2410	C, Ta, F	Bronchopneumonia, squames ++	Normal	Normal	Inflammatory reaction in placenta and cord placentitis

Ossification centres C=calcaneum Ta=talus, F=lower end of femur Ti= upper end of femur, cuboid
C D H =congenital dislocation of the hip ++=many, ±=few

TABLE III—BACTERIOLOGY

Case no	Interval from death to bacteriological examination	Bacteriological examination of infant							Bacteriological examination of mother							Interval from delivery to bacteriological examination
		Lung	Spleen	Sensitivity					Nose and Throat	Vagina	Sensitivity					
				Penicillin	Tetracycline	Erythromycin	Streptomycin	Chloramphenicol			Penicillin	Tetracycline	Erythromycin	Streptomycin	Chloramphenicol	
1	4 days	*Staph pyogenes*	Negative	R	S	S	S	S	Negative	Negative						5 days
2	3 days	*Staph pyogenes*	Positive	S	S	S	S	S	Negative	*Staph pyogenes*	S	S	S	S	S	2 days
3	2 days	*Staph pyogenes*	Negative	R	S	S	S	S	Negative	Negative						73 days
4	4 days	*Staph pyogenes*	Negative	R	S	S	S	S								Not made
5	2 days	*Staph pyogenes*	Negative	R	S	S	S	S								Not made
6	3 days	*Staph pyogenes*	Negative	S	S	S	S	S	Negative	Negative						5 days
7	6 days	*Staph pyogenes*	Negative	R	S	S/R	R	S	Negative	*Staph pyogenes*	R	S	S/R	R	S	2 days
8	2 days	*Staph pyogenes*	Negative	S	S	S	S	S	Negative	*Staph pyogenes*	S	S	S	S	S	Same day

S=sensitive R=resistant

for the view that inhalation was the route of pneumonic infection is provided by the occurrence of fœtal distress, and the presence of numerous amniotic squames in the air-passages of all infants in which this route is postulated A vaginal route of infection is also supported by the fact that an undue number of vaginal procedures were made in the antenatal period, these were carried out because of a high incidence of antenatal complications in these mothers (table I)

The sensitivity of the organisms to various antibiotics is shown in table III Three strains were sensitive to all the antibiotics against which they were tested These three organisms were probably derived from the mothers themselves, or from a newly introduced strain carried into the ward Case 8 (table I) is typical, a high vaginal swab from the mother before delivery showed a sensitive strain of *Staph pyogenes*

In three cases the mother's vagina did not grow *Staph pyogenes* though it was isolated from the fœtal lungs However, the interval of several days between delivery and taking a vaginal swab may explain this discrepancy

Cases 4 and 5 (table I) were infants with congenital abnormalities They survived much longer than all other infants in this series The organism responsible for their pneumonia had the same resistance pattern as the indigenous hospital staphylococcus They were probably infected post partum There were no inflammatory changes of the umbilical cord or placenta in case 4 The other placenta was not available

Three cases showed œsophagitis, associated with intubation and the administration of gastric oxygen The lesion was probably incidental, and was not the primary source of infection

All infants were premature as judged by weight The number of ossification centres found at necropsy varied from case to case (table III) Most were found in case 5—an infant with multiple congenital abnormalities This suggests that such babies may be expected to develop lung infections, either because prematurity reflects antenatal complications and the need for excessive manipulations, or because they are unduly susceptible to infection

Summary

Eight cases of fatal staphylococcal pneumonia in neonates are described The infection was often fulminant, and a variety of histological appearances—ranging from extensive intra-alveolar hæmorrhage with necrosis of the alveolar walls to a slight polymorphonuclear leucocytic infiltration—were found post mortem

The causal organism in every case was *Staphylococcus pyogenes* It is suggested that in six of the infants the bronchopneumonia was due to the inhalation of infected amniotic fluid, two cases were probably infected post partum The need for diligent application of aseptic methods in the care of the newly born is stressed

Our thanks are due to Dr A M Barrett, Dr D M T Gairdner, and Dr M H Gleeson-White for their cooperation in the preparation of this paper

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GONADAL DYSGENESIS (TURNER'S SYNDROME) WITH MALE PHENOTYPE AND XO CHROMOSOMAL CONSTITUTION

WALTER BLOISE
M.D. São Paulo

L. M. DE ASSIS
M.D. São Paulo

CASSIO BOTTURA
M.D. Ribeirão Preto

IRIS FERRARI
M.D. Ribeirão Preto

From the Department of Endocrinology and Metabolic Disorders, Faculty of Medicine, São Paulo, and the Department of Clinical Medicine, Faculty of Medicine, Ribeirão Preto, Brazil

A boy, aged 8, the eldest son of young parents, was admitted to the metabolic department on April 5, 1957, because of poor somatic development.

Maternal pregnancy and labour had been normal. General condition was fair. Height 3 ft. 9 in. (113 cm.), weight 45 4 lb (20·6 kg.), span 3 ft. 7 in. (110 cm.) (fig 1). Clinical examination revealed malformed external genitalia and some lesser congenital defects—low hair-line and ears, high-arched palate, and a number of naevi. The penis 1 2 in. (3 1 cm.) long, without urethral meatus, was bent ventrally by a web connecting the ventral surface to the perineum. Thus the "scrotum" appeared to be bifid, a depression with two small meatuses being visible in the midline, one communicated with the bladder through a short urethra, and the other led to a closed cavity (fig 2). When the patient underwent plastic surgery, it was verified this cavity communicated with the uterus. No testes could be felt in the labioscrotal folds or in the inguinal regions. A rudimentary uterus was seen on peritoneoscopy and a laparotomy was done for further investigation of the internal genitalia. Near the small left tube was an elongated, almond-shaped mass ³⁄₈ in. (1 cm.) long, which was histologically a rudimentary testis (figs. 3 and 4). On the right, instead of an ovary, there was connective tissue, as seen in other cases of gonadal dysgenesis with negative chromatin pattern (Epps et al. 1958). 17-ketosteroids (Drekter) 0·8 mg. per 24 hours. Bone age of 7 years, X-ray examination of the skull, no abnormality. Colour-vision normal (Ishihara tests).

The nuclear sex in material obtained from the blood, oral smears, and from the skin biopsy was male. In the blood-smears, no "drumsticks" were found in 500 leucocytes counted. Chromosomal counts (Bottura and Ferrari 1960) in the 20 bone-marrow specimens examined gave a constant number of 45 chromosomes. In the 13 cells in optimal condition, 4 small acrocentric chromosomes could be positively identified. After pairing (fig 5), the absence of a second medium-sized chromosome with subcentral centromere (probably an X chromosome) was noted. In view of these facts, the chromosomal constitution of the patient must be XO. The constancy of the number 45 in the chromosomal counts argues against

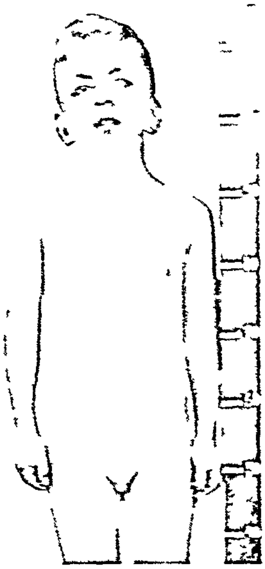

Fig 1

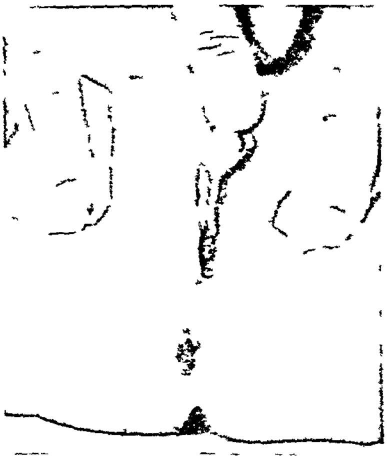

Fig 2.

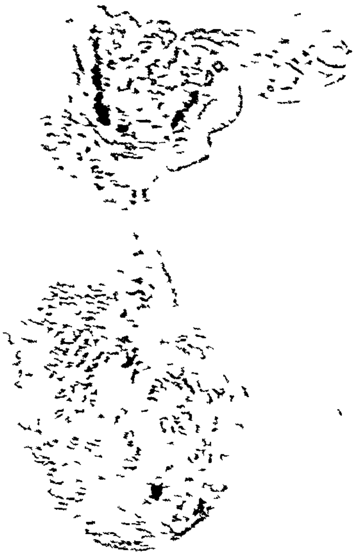

Fig 3.

Fig 1—Gonadal dysgenesis (Turner's syndrome) in a boy aged 8.

Fig 2—The external genitalia.

Fig 3—Embryonic testis.

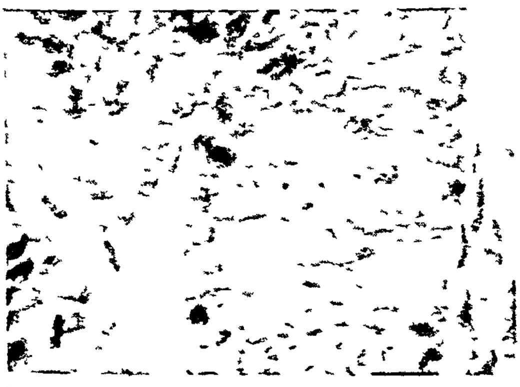

Fig 4—Testicular tissue showing Sertoli cells, some undifferentiated germ cells, and spermatogonia. No later phases can be identified. Scanty and isolated interstitial cells are present. (Hæmatoxylin and eosin. × 220.)

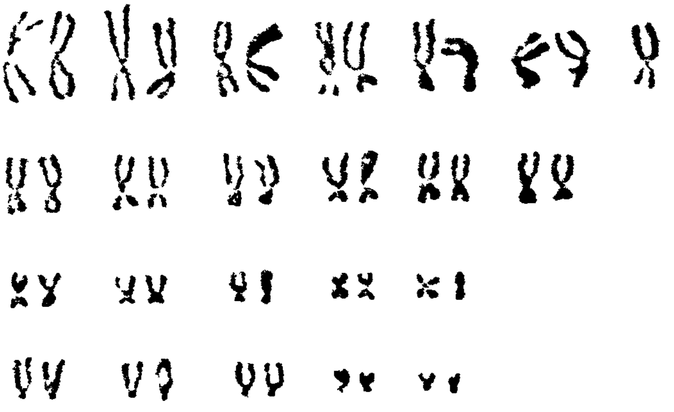

Fig 5—Paired chromosomes from bone-marrow specimen showing absence of one X chromosome.

the possibility of mosaicism as far as bone-marrow cells are concerned

Discussion

XO chromosomal constitution in gonadal dysgenesis with female phenotype was described by Ford et al (1959) A reasonable assumption from the study of our case is that XO chromosomal constitution is not incompatible with a male phenotype and with the presence of embryonic testis Further instances of testicular development with a male phenotype without Y chromosome are represented by the XX true hermaphrodites recently reported (Harnden and Armstrong 1959, Hungerford et al 1959, de Assis et al 1960, Ferguson-Smith et al 1960)

Summary

We describe a case of gonadal dysgenesis (Turner's syndrome) in a boy of 8 He had a rudimentary uterus, and an embryonic testis No ovaries were found The nuclear sex was male "Drumsticks" were absent from the leucocytes Only 45 chromosomes were present in the cells of all (20) bone-marrow specimens examined, and chromosome analysis pointed to the absence of one X chromosome His phenotype is, therefore, male with an XO chromosomal constitution

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PREMEDICATION WITH ATROPINE BY MOUTH

M C JOSEPH
M D Cantab , M R C P , D C H
ASSISTANT TO THE DIRECTOR OF THE DEPARTMENT OF CHILD HEALTH

R J VALE
M B Lond , M R C P E , F F A R C S
CONSULTANT ANÆSTHETIST

GUY'S HOSPITAL, LONDON, S E 1

IN 1872 Heidenhain demonstrated that the salivary secretion produced by stimulation of the chorda tympani was prevented by atropine, and, in the next year, Ebstein used it therapeutically in a patient with apoplexy In 1875 Munro reported its use in cats for preventing early cardiac arrest during chloroform anæsthesia, but it was not until after 1890 that the subcutaneous injection of atropine before induction of anæsthesia came into general use in this country

There seems to be no record of the oral administration of atropine before operation, though it is used therapeutically for various conditions Even when sedative drugs are given by mouth preoperatively, it has still been common practice to inject atropine, though Dr W S McConnell tells us he has used it by mouth effectively In children it is especially desirable to avoid injections, hence we conducted this trial of the effect of atropine given by mouth

The Trial

All children admitted to the Evelina Hospital, under the same surgeon and anæsthetist for tonsillectomy, were included in the trial When admitted, the day before the operation, the child was placed in an "oral" or "subcutaneous" group by random allocation, the anæsthetist being unaware of the grouping The trial lasted fifteen months, and ended when the anæsthetist ceased to work at this hospital

240 children were admitted to the trial, but 93 were excluded because a different anæsthetist was working on that occasion or because the data were incomplete There remained 147 children for study Their sex, average weights, and ages were

	No	*Males*	*Females*	*Age (yr)*	*Weight (lb)*
Oral	74	41	33	6 5	49
Subcutaneous	73	39	34	6 7	51

and the age-distribution was

	No	*3–5 yr*	*6–8 yr*	*9–12 yr*
Oral	74	21	44	9
Subcutaneous	73	17	45	11

The average interval between administration of atropine and induction of anæsthesia was 95 and 87 minutes for the oral and subcutaneous groups respectively

During the night before operation the sleeping pulse was measured twice Next morning, an hour before the expected time of operation, atropine was given—either 0 85 mg by mouth or 0 64 mg subcutaneously—with butobarbitone, in a dose of 75 mg per stone body-weight The pulse-rate was recorded again just before the child was taken to the operating-theatre, and the state of consciousness was noted In the anæsthetic-room the size of the pupils was measured to the nearest millimetre by comparison with a prepared scale, and the reaction to light was noted All patients were anæsthetised with ether after induction with either ethyl chloride on a Schimmelbusch mask or nitrous oxide and oxygen through a semiopen circuit The degree of salivation was assessed during induction by inserting a finger into the buccal sulcus, if it was dry or slightly moist, it was recorded as O, if wet but not dripping off the finger as +, and if copious and stringy as ++ Additionally, if salivation interfered with induction, it was recorded as ++

Results

Salivation

The degree of salivation was

	No	*O*	*+*	*++*
Oral	74	63	9	2
Subcutaneous	73	68	4	1

Excessive salivation was uncommon in either group, occurring only twice in the oral group and once in the subcutaneous group There was a little more mild salivation in the oral group than in the subcutaneous group, but the difference was small and not significant at the 5% level

Pupils

The average size of the pupils was identical in the two groups, and the incidence of negative reaction to light was similar

	No	*Size (mm)*	*Negative reaction*
Oral	74	6 1	15 (*19%*)
Subcutaneous	73	6 1	11 (*15%*)

Pulse-rate

The response of the pulse-rate was

	No	*Before atropine*	*After atropine*	*Rise*
Oral	74	85	107	22
Subcutaneous	73	86	111	25

The mean rate before atropine was similar in both groups, there being a rise of 22 and 25 beats per minute in the oral and subcutaneous groups respectively

Discussion

Dose

Unna et al (1950) have shown that the smallest effective dose of atropine for suppression of salivation in children aged 3–12 years is about 0 007 mg per kg body-weight subcutaneously, or three times this dose by mouth The dose for a 20 kg child is about a quarter the dose of

0 64 mg commonly used subcutaneously Mushin and Galloon (1953) also regard 0 64 mg subcutaneously as more than is needed to suppress salivation Thus our subcutaneous dose was probably three times larger than necessary, and our oral dose was the smallest effective dose recommended by Unna et al

Salivation

Although we evaluated the effect of atropine by several criteria, the suppression of salivation is especially important in premedication, and is also the most sensitive index of the effect of atropine (Unna et al 1950) Our finding of excessive salivation in 2% was similar to the 4% observed by Marx and Orkin (1959), but their figures were for atropine and scopolamine, and they pointed out that their atropine group had more secretion than their scopolamine group

During our study atropine was deliberately not given to a few patients, in order to establish that it had some effect But the excessive salivation and extreme bradycardia in the first five children so treated made us unwilling to continue, and we resumed the trial Mushin and Galloon (1953) pointed out that the degree of salivary depression necessary depended on the type of anæsthesia used, ether needing about 40% and nitrous oxide about 10% depression We used ether, and therefore our patients needed maximum depression of salivation

Pupils and Pulse-rate

Both mydriasis and tachycardia are unreliable signs of the effect of atropine, because anxiety, excitement, or barbiturates may also produce these signs, but atropine was probably responsible for mydriasis in some of our patients, as the correlation between size of pupil and reaction to light was significant

	No	*Size of pupil (mm) with positive reaction*	*No*	*Size of pupil (mm) with negative reaction*
Oral	59	5 7±0 19	15	7 8±0 82
Subcutaneous	62	5 8±0 19	11	8 1±0 96

Difference in size of pupils is significant ($P = <0\ 05 > 0\ 02$)

We cannot be sure that the rise of pulse-rate was solely due to atropine, although it probably made a substantial contribution. The rise in pulse-rate was similar in both our groups

We were unable to show any correlation between pupil size, rise in pulse-rate, and salivation However, we found correlation between the size of pupil and its response to light, the fixed pupils having a mean diameter of 7 8 and 8 1 mm (oral and subcutaneous) compared with 5 7 and 5 8 mm for the active pupils It is interesting that we found this correlation in the oral group, for Unna et al (1950) pointed out that the smallest dose by mouth which suppressed salivation did not cause mydriasis or tachycardia

The average time between giving atropine and inducing anæsthesia was 95 and 87 minutes in the two groups This interval is similar to that observed by Unna et al (1950), who found the greatest effect of atropine was between sixty and a hundred and twenty minutes for an oral group, and to that of Mushin and Galloon (1953), who found the greatest effect between sixty and ninety minutes for a subcutaneous group

Our investigation has shown that, in children, atropine given by mouth is as effective as atropine given by subcutaneous injection As it is desirable to avoid injection in children, the oral route seems preferable

Summary

147 children randomly selected were given oral or subcutaneous atropine before anæsthesia, and the effects on salivation, pupils, pulse-rate, and anæsthesia were observed No differences between the groups were found

Thus is it concluded that atropine by mouth is satisfactory for premedication

We wish to thank the nursing staff and residents at the Evelina Children's Hospital for their help, and Mr L F W Salmon for allowing us to conduct this trial on patients under his care

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Preliminary Communications

ANTINUCLEAR FACTORS IN THE SERUM OF RELATIVES OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

DURING an investigation of antinuclear factors in the serum of patients with systemic lupus erythematosus (S L E) we found a relationship between the titre of antinuclear factors in the serum and the clinical activity of the disease High titres were found in patients with active S L E , the titres were considerably lower in most patients in whom the disease was adequately controlled by treatment with prednisone [1] As this test for antinuclear factors was sensitive, and as the results could be quantitated, we were prompted to examine the serum of relatives of patients with S L E for antinuclear factors, particularly in view of recent reports of the familial occurrence of S L E [2–8]

MATERIAL AND METHODS

Smears of fresh unfixed healthy human buccal mucosal epithelial cells were used as the source of the cell nuclei After washing with 0 01 *M* saline phosphate buffer (pH 7 0) the slides were air-dried, and the smears were covered with a drop of the test serum The smears were incubated for 90 minutes at room temperature in a moist atmosphere The slides were washed for 30 minutes in three changes of buffer, air-dried, and layered for 30 minutes with rabbit antihuman γ-globulin conjugated with fluorescein isothiocyanate (Sylvana) They were washed and were then mounted in buffered glycerin They were inspected for specific nuclear fluorescence, using a Reichert Zetopan microscope with an aplanatic dark field condensor (light source Osram HBO 200 mercury-vapour lamp, Corning 5840 and Wratten 2A filters)

All tests were done in duplicate When specific nuclear fluorescence was found, serial dilutions of serum (to 1 4096) were incubated with smears of buccal mucosal cells in a similar fashion The highest dilution in which specific nuclear fluorescence was detected was called the ' titre " of antinuclear factors

Full details of the technique and controls used will be published elsewhere [1] It was shown that duplicate titrations on the same sera gave identical titres in 4 of 10 instances The final titres differed by only one dilution in the other 6

RESULTS

The results are shown in table I Single serum samples from 40 healthy subjects and 50 sera from 45 patients with

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TABLE I—TITRES OF ANTINUCLEAR FACTORS IN HEALTHY SUBJECTS, IN PATIENTS WITH VARIOUS DISEASES UNRELATED TO S L E, AND IN PATIENTS WITH S L E AND THEIR RELATIVES

Titre of Antinuclear factors (dilution)	Healthy subjects	Diseases unrelated to S L E	Patients with S L E	Relatives of patients with S L E
Negative				
Undiluted	33	40	3	20
1 1	3	5	2	3
1 2	4	4	1	3
Positive				
1 4 to 1 16	0	1	12	17
1 32 to 1 128	0	0	14	4
1 256 to 1 4096	0	0	19	3

diseases unrelated to S L E were studied as controls Specific nuclear fluorescence was not seen with 73 of these sera, and was seen with undiluted serum or serum diluted 1 2 in another 16 sera In only 1 instance was specific nuclear fluorescence seen when the serum was diluted 1 4

51 patients with S L E were studied When the first serum drawn from each of these patients was examined, specific nuclear fluorescence was found with serum diluted 1 4 or higher in 45 In all, 151 specimens of serum from these 51 patients have been examined to date, and specific nuclear fluorescence with serum diluted 1 4 or higher was observed with 131 specimens As antinuclear factors were found when the serum was diluted 1 4 in only 1 of 90 sera examined as controls, the demonstration of antinuclear factors in serum diluted 1 4 or more appeared to distinguish patients with S L E from healthy subjects and those with a variety of other diseases The test was therefore called positive when antinuclear factors were demonstrated in serum diluted 1 4 or more

TABLE II—RESULTS OF TESTS FOR ANTINUCLEAR FACTORS IN THE RELATIVES OF PATIENTS WITH SYSTEMIC LUPUS ERYTHMATOSUS

Relationship	Female relatives		Male relatives	
	Positive tests	Negative tests	Positive tests	Negative tests
Parents	5	1	0	4
Siblings	6	4	4	5
Offspring	2	0	2	3
Maternal siblings	3	1	1	1
First cousins	1	0	0	1
Grandparents	0	3	0	3
Totals	17	9	7	17

Single serum samples from 50 members of families of 12 patients with S L E were studied (tables I and II) Specific nuclear fluorescence was demonstrated with serum diluted 1 4 or more in 24 instances Positive tests were found with the sera of 19 of 36 first-degree relatives tested, and with the sera of 5 of 14 second-degree relatives Positive tests were found in 17 of 26 female relatives but in only 7 of 24 male relatives The difference in the frequency of positive tests in male and female relatives is significant (χ^2=5 2, P= <0 05), but further observations on this difference are necessary

Two family pedigrees are shown in fig

In the first pedigree the propositus (II 4) a 15-year-old schoolgirl in whom defin clinical evidence of S L E had been found, an in the past, Hargraves' cells had been demonstrated in her blood Findings diagnostic o lupus nephritis were observed in a renal biops 4 specimens of serum were tested for antinuclear factors when the patient was symptom-free as a result of treatment with prednisone, all were negative Positive tests for antinuclear factors were found in the mother (I 1) and 3 of 5 siblings—in 1 of whom (II 1) the titre was 1 1024

In the second pedigree the propositus (II 2) was a 21-year-old American Negro housewife with typical S L E Positive tests for antinuclear factors were found in the serum of the patient, her 2 younger sisters, her 5-year-old son, and 3-year-old daughter (III 3)—in whom the titre of antinuclear factors was 1 4096

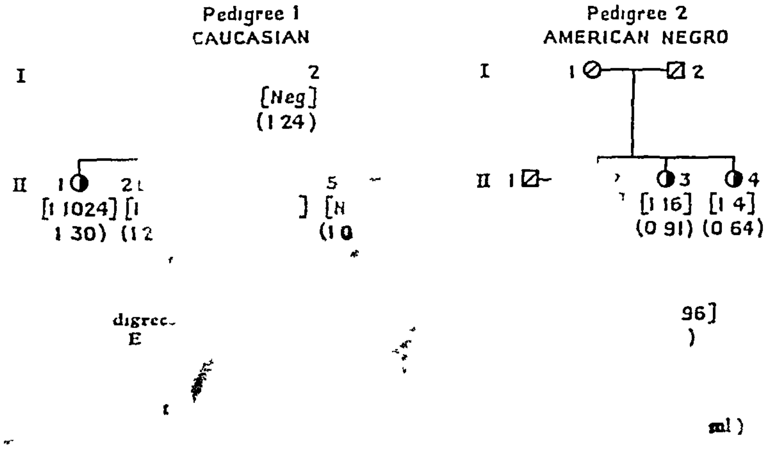
The serum-γ-globulin levels were estimated by the Biuret reagent and filterpaper electrophoresis They are compared in fig 2 with values from 62 healthy Caucasian (1 13±0 23 g per 100 ml) and 62 healthy American Negro subjects (1 37±0 30 g per 100 ml) Elevated γ-globulin levels (>2 S D above the mean of the controls) were found in only 3 Caucasian relatives and 2 Caucasian controls Decreased γ-globulin levels (>2 S D below the *mean of the controls) were found in* 1 Caucasian *and* 2 Negro relatives 5 of the 6 Negro relatives were members of one family (pedigree 2) The difference between the γ-globulin levels in the members of this family and those in the controls was significant (χ^2=17 2, P= <0 01)

DISCUSSION

In 1957 Leonhardt [2] reported S L E in 3 of 14 siblings He pointed out that at that time there were only four reported instances of the familial occurrence of S L E

Subsequently, Agranat et al [3] Larsson and Leonhardt,[4] and Lawrence [5] have each reported S L E in 2 sisters Wagenhals and Burgeson [6] observed the disease in twin sisters Griffin et al [7] found S L E in a father and his daughter, and Holman and Deicher [8] reported its occurrence in a mother and her daughter These clinical observations suggested that S L E may possibly be a familial disorder

In a study of two pedigrees, Larsson and Leonhardt [4] found higher mean serum-γ-globulin levels in siblings of patients with S L E and their children than in controls living under the same environmental conditions The siblings had higher mean γ-globulin values than the first cousins, and the siblings' children than the second cousins Larsson and Leonhardt considered that familial hypergammaglobulinæmia and familial S L E were possibly closely related and were manifestations of an underlying, genetically determined tendency to overproduction of γ-globulin Holman and Deicher [8] found "distinct hypergammaglobulinæmia" in 11 of 57 relatives from 18 families of patients with S L E, and Rodnan et al [9] found definite hypergammaglobulinæmia in 12 of 59 relatives, thus confirming the observations of Larsson and Leonhardt



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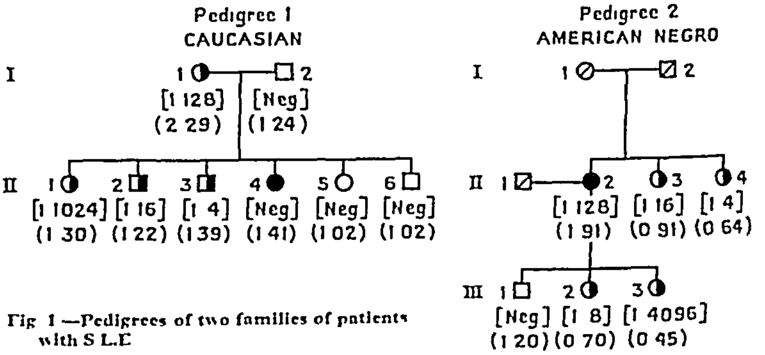

Fig 1—Pedigrees of two families of patients with S L E

● S L E
◐ —positive test for antinuclear factors
○ —negative test for antinuclear factors
⊘ —not tested
[ ] —titre of antinuclear factors
( ) —serum γ globulin (g per 100 ml)

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9 Rodnan G P Maclachlan M J, Creighton, A S *Clin Res* 1960, 8, 197

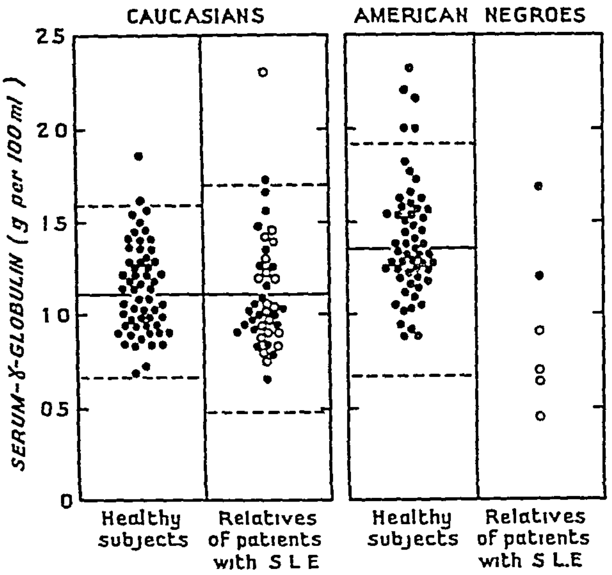

Fig 2.—Serum-γ-globulin levels in healthy subjects and in relatives of patients with S.L.E.

The mean values are given by continuous lines and two standard deviations by interrupted lines

○ = patients with positive tests for antinuclear factors
● = patients with negative tests for antinuclear factors

We found few relatives with hypergammaglobulinæmia, but somewhat high γ-globulin levels were found in 5 of 7 members of pedigree 1 Unusually low γ-globulin levels were found in 4 of 5 members of pedigree 2 This finding is of interest in view of the reported development of an arthritis resembling rheumatoid arthritis in almost half of 16 children with the congenital form of agammaglobulinæmia, and of collagen disease in patients with congenital and acquired agammaglobulinæmia [10]

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VICTOR E POLLAK*
M B W'srand, M.R C P.E
ENNO MANDEMA†
M.D Groningen
ROBERT M KARK
F R C P, F A C P

Departments of Medicine,
Presbyterian-St Luke's Hospital,
Cook County Hospital,
Research and Educational Hospitals,
University of Illinois College of Medicine,
Chicago, Illinois, U S.A

BLOOD-GROUP DISTRIBUTION IN MEGALOBLASTIC ANÆMIA OF PREGNANCY

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Folic-acid deficiency in pregnancy can thus be conveniently classified in four categories

Grade 0—The marrow remains entirely normoblastic and folic-acid depletion can be diagnosed with certainty only by folic-acid assays In these cases the hæmoglobin level can usually be raised by folic-acid therapy

Grade 1—The mildest form of megaloblastic anæmia, in which the marrow is predominantly normoblastic, though it contains a number of transitional megaloblasts Diagnosis in such cases may need confirmation by other criteria—e g, a raised serum-iron level and satisfactory response to folic-acid therapy

Grade 2—The marrow is predominantly megaloblastic, but the majority of cells is of the transitional type.

Grade 3—A florid megaloblastic marrow in which the classical Ehrlich type of megaloblast predominates The marrow picture in these cases is indistinguishable from that seen in addisonian anæmia

Obviously, the marrow-changes in these four categories reflect, to some extent, the degree of folic-acid depletion in any given person It would be an oversimplification to assume from this that all pregnant women with folic-acid

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Undiluted	33	40	3	20
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1 4 to 1 16	0	1	12	17
1 32 to 1 128	0	0	14	4
1 256 to 1 4096	*0*	*0*	*19*	*3*

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51 patients with S L E were studied When the first serum drawn from each of these patients was examined, specific nuclear fluorescence was found with serum diluted 1 4 or higher in 45 In all, 151 specimens of serum from these 51 patients have been examined to date, and *specific nuclear fluorescence with serum diluted 1 4* or higher was observed with 131 specimens As antinuclear factors were found when the serum was diluted 1 4 in only 1 of 90 sera examined as controls, the demonstration of antinuclear factors in serum diluted 1 4 or more appeared to distinguish patients with S L E from healthy subjects and those with a variety of other diseases The test was therefore called positive when antinuclear factors were demonstrated in serum diluted 1 4 or more

TABLE II—RESULTS OF TESTS FOR ANTINUCLEAR FACTORS IN THE RELATIVES OF PATIENTS WITH SYSTEMIC LUPUS ERYTHMATOSUS

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	Positive tests	Negative tests	Positive tests	Negative tests
Parents	5	1	0	4
Siblings	6	4	4	5
Offspring	2	0	2	3
Maternal siblings	3	1	1	1
First cousins	1	0	0	1
Grandparents	0	3	0	3
Totals	17	9	7	17

Single serum samples from 50 members of families of 12 patients with S L E were studied (tables I and II) Specific nuclear fluorescence was demonstrated with serum diluted 1 4 or more in 24 instances Positive tests were found with the sera of 19 of 36 first-degree relatives tested, and with the sera of 5 of 14 second-degree relatives Positive tests were found in 17 of 26 female relatives but in only 7 of 24 male relatives The difference in the frequency of positive tests in male and female relatives is significant (χ^2=5 2, P= <0 05), but further observations on this sex difference are necessary

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In the first pedigree the propositus (II 4) was a 15-year-old schoolgirl in whom definite clinical evidence of S L E had been found, and, in the past, Hargraves cells had been demonstrated in her blood Findings diagnostic of lupus nephritis were observed in a renal biopsy nuclear factors when the patient was symptom-free as a result of treatment with prednisone, all were negative Positive tests for antinuclear factors were found in the mother (I 1) and 3 of 5 siblings—in 1 of whom (II 1) the titre was 1 1024

In the second pedigree the propositus (II 2) was a 21-year-old American Negro housewife with typical S L E Positive tests for antinuclear factors were found in the serum of the patient, her 2 younger sisters, her 5-year-old son, and 3-year-old daughter (III 3)—in whom the titre of antinuclear factors was 1 4096

The serum-γ-globulin levels were estimated by the Biuret reagent and filterpaper electrophoresis They are compared in fig 2 with values from 62 healthy Caucasian (1 13±0 23 g per 100 ml) and 62 healthy American Negro subjects (1 37±0 30 g per 100 ml) Elevated γ-globulin levels (>2 S D above the mean of the controls) were found in only 3 Caucasian relatives and 2 Caucasian controls Decreased γ-globulin levels (>2 S D below the mean of the controls) were found in 1 Caucasian and 2 Negro relatives 5 of the 6 Negro relatives were members of one family (pedigree 2) The difference between the γ-globulin levels in the members of this family and those in the controls was significant (χ^2=17 2, P= <0 01)

DISCUSSION

In 1957 Leonhardt [2] reported S L E in 3 of 14 siblings He pointed out that at that time there were only four reported instances of the familial occurrence of S L E

Subsequently, Agranat et al [3] Larsson and Leonhardt,[4] and Lawrence [5] have each reported S L E in 2 sisters Wagenhals and Burgeson [6] observed the disease in twin sisters Griffin et al [7] found S L E in a father and his daughter, and Holman and Deicher [8] reported its occurrence in a mother and her daughter These clinical observations suggested that S L E may possibly be a familial disorder

In a study of two pedigrees, Larsson and Leonhardt [4] found higher mean serum-γ-globulin levels in siblings of patients with S L E and their children than in controls living under the same environmental conditions The siblings had higher mean γ-globulin values than the first cousins, and the siblings' children than the second cousins Larsson and Leonhardt considered that familial hypergammaglobulinæmia and familial S L E were possibly closely related and were manifestations of an underlying, genetically determined tendency to over-production of γ-globulin Holman and Deicher [8] found "distinct hypergammaglobulinæmia" in 11 of 57 relatives from 18 families of patients with S L E, and Rodnan et al [9] found definite hypergammaglobulinæmia in 12 of 59 relatives, thus confirming the observations of Larsson ahd Leonhardt

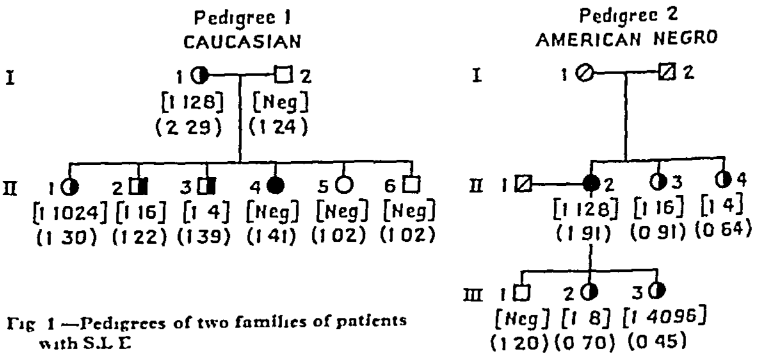

Fig 1—Pedigrees of two families of patients with S.L E

● =S L E

◐ —positive test for antinuclear factors

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9 Rodnan, G P, Maclachlan M J, Creighton A S *Clin Res* 1960 8, 197

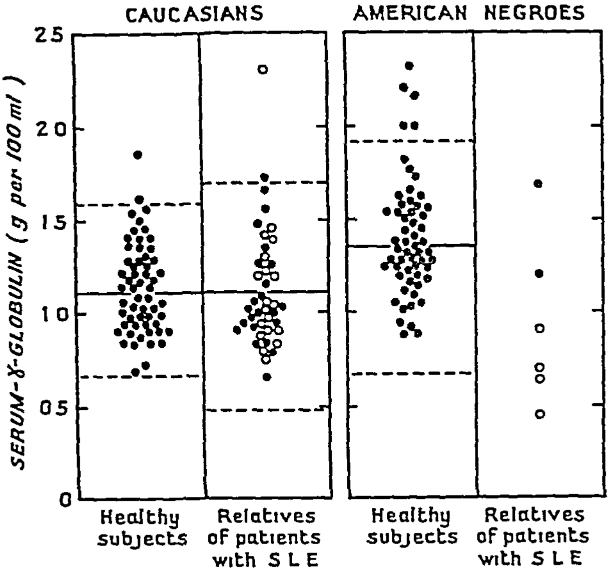

Fig 2.—Serum-γ-globulin levels in healthy subjects and in relatives of patients with S.L.E.

The mean values are given by continuous lines and two standard deviations by interrupted lines.

○ = patients with positive tests for antinuclear factors
● = patients with negative tests for antinuclear factors

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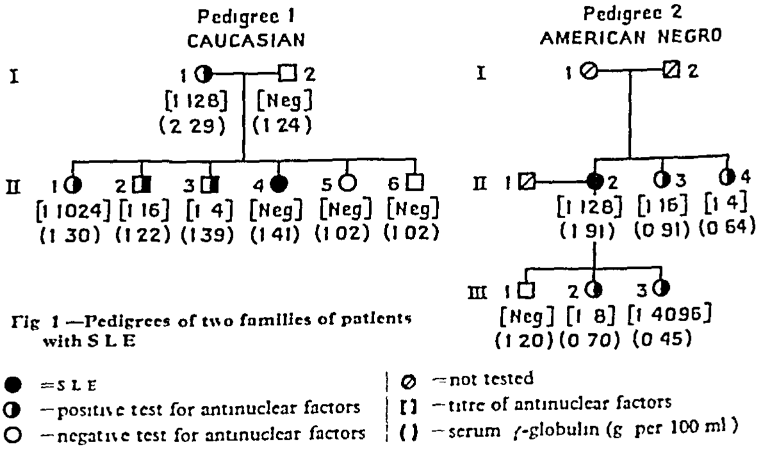

Fig 1 —Pedigrees of two families of patients with S L E

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9 Rodnan G P Maclachlan, M J Creighton, A S *Clin Res* 1960, 8, 197

Cooling and rewarming is by means of a heat-exchanger constructed from stainless steel. A filter and bubble trap are incorporated in the arterial outflow line. Two sucker lines are provided which deliver their blood on to five perforated plates lightly coated with anti-foam. The output of the arterial pump and of the pump controlling the suction lines can be varied by two simple hand controls. The apparatus and tubing in contact with blood is sterilised in ethylene oxide for 24 hours before use.

The hypothermic and heating equipment is contained within a low trolley which acts as a mount for the heart-lung machine. In this way the apparatus, while remaining compact, is entirely self-contained. The cold source is supplied with a mixture of ice and water kept in a lagged 2 gal. tank, and hot water is kept thermostatically controlled at about 40°C in a separate tank.

Application

The apparatus has been used in twenty-five dog experiments. In addition, four children have been operated on, with one death. In use the machine requires very little adjustment, the running being in the hands of one technician.

The apparatus has been constructed for me by Mr. A. F. Turner in the Guy's Hospital Medical School workshop, and it will be available through Cardiac Recorders, Ltd., Weymouth Street, London, W.1.

Guy's Hospital,
London, S.E.1

D. N. ROSS
M.B., B.SC. Cape Town, F.R.C.S.

Reviews of Books

Medical and Dental Aspects of Fluoridation

W. A. CANNELL, M.R.C.S., D.P.H., L.D.S. London: Lewis. 1960. Pp. 125. 15s.

MOST of the growing literature of fluoridation and fluorine is scattered in various journals. A great deal of the research has been done in the United States, and the few books that have appeared since Roholm's classic text in 1937 have been published there. A British survey of the present state of knowledge is welcome, and Dr. Cannell gives a concise and readable summary, with an account of some important original work on the effect of trace elements.

It is a relief to find a book that deliberately does not discuss the various fluoridation trials in the United States. So much has been written about them and their real and alleged shortcomings that there is a risk of losing sight of one of the fundamental issues—the physiological and biochemical effects of fluorides. Too little is generally known about the systemic effects of fluorides, and Dr. Cannell's book should go a long way towards dispelling this ignorance, especially among the opponents of fluoridation.

The chapters on the pharmacology of the fluorides and on the calcification of skeletal and dental tissues are particularly good. Speculation is kept to a minimum, and the facts are presented fairly, and without bias. Not everyone will agree with Dr. Cannell in his excursion into the field of logical causality (p. 69), but the inescapability of fluorides renders his argument an attractive one.

The final chapter, on the public-health aspects, puts forward a well-reasoned case for the fluoridation of water-supplies. Other possible means of administration are discussed in the light of recent research. The bibliography is comprehensive and up to date, though there is no reference to Mackenzie's extensive review.[1]

This is probably one of the best accounts of fluorides and their effects that has been published for some time.

Pathology of Infancy and Childhood

AGNES R. MACGREGOR, M.D., F.R.C.P.E., F.R.C.O.G., reader in pathology, Edinburgh University. Edinburgh and London: E. & S. Livingstone. 1960. Pp. 631. 75s.

A VOLUME concerned entirely with pædiatric pathology has been urgently needed by many pathologists, and the gap has been partly filled by this book in which Dr. Macgregor incorporates the experience of her many years as an authority on this subject. It is a simple book: it makes no pretension to being a work of reference for pædiatric pathologists, but has been designed for the pathologist whose main work and interests are with older patients. Most conditions which he is likely to meet are considered adequately, with proper regard for their relative importance and incidence. Bearing in mind that the great majority of necropsies are on infants dying in the perinatal period, notes on necropsy technique and detailed practical accounts of perinatal conditions are included. Many facts in this part of the book rarely appear in print and are usually appreciated only after considerable experience. The section dealing with developmental anomalies could have been fortified by the inclusion of notes on embryology, supported by diagrams. Since many hospitals have cardiothoracic units, and deaths from cardiovascular anomalies often form a big part of pædiatric necropsy work, the account of these anomalies may be too superficial. Although the photographs of specimens of malformed hearts are generally self-explanatory, a few diagrams would have enhanced clarity. A lack of uniformity between different sections of the book is mainly due to the omission of conditions which are not peculiar to infants or children, or which are well described in standard textbooks of pathology. But a few relatively important diseases are treated rather briefly, and many less common conditions are not mentioned even by reference to the literature. Although the references are well chosen and up to date, the bibliography will be little help to the pathologist faced with an unusual case.

This book will be particularly useful to those embarking upon a career in pathology or pædiatrics. Its value to the established pathologist is limited, but it will be enjoyed by those who appreciate the signs of the author's wide experience.

The Chemical Senses in Health and Disease

H. KALMUS, SC.D., M.D., reader in biology, University of London; S. J. HUBBARD, B.SC., PH.D., lecturer in physiology, University College, London. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 95. 30s.

NO disciple of Brillat-Savarin needs to be reminded of the importance of the chemical senses—concerned as they are with taste and smell. But many may be surprised at the complexity of the physiological processes subserving the art of transcendental gastronomy. Who would have suspected, for instance, that over 60 volatile substances contribute to the aroma of coffee? This suggests almost endless permutation of naturally occurring odours and many kinds of odour-receptors. On the other hand, only four basic tastes—sour, salt, sweet, and bitter—are firmly established. The interplay of taste and smell, the importance of these chemical senses in behaviour both in animals and man, some curious and interesting genetical variations in both senses, and lines of future research and their practical importance are all discussed in this book. The psychological aspects—in some ways the most fascinating of any—are also briefly mentioned. The book is short and well worth the attention of physiologist and clinician. It is a pity the price is so high.

The Early History of Surgery

W. J. BISHOP, editor, *Medical History*. London: Robert Hale. 1960. Pp. 192. 18s.

AT a time when road travel is becoming increasingly dangerous, it is good to discover that some at least of its former hazards have been mitigated. Richard Wiseman, writing in 1676, described the misadventure which befell "a gentleman of about thirty years of age, who was coming out of Hertfordshire through Tottenham and riding upon the causeway near an inn when, one emptying a chamber pot out of the window

deficiency are equally liable to develop advanced megaloblastic anæmia A study of the blood-group distribution of patients with megaloblastic anæmia of pregnancy has shown that cases with a grade-3 type of marrow, in which the classical Ehrlich type of megaloblasts are encountered, probably represent a special group which appears to be genetically determined

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[1] Mackenzie, E. F. W. *Lancet*, 1952, i, 961.

The blood-group distribution of 175 patients with megaloblastic anæmia of pregnancy was compared with that of 3500 routine antenatal cases in the same district As seen in table I, the only deviation from the norm is an increase in the incidence of blood-group A in patients with megaloblastic anæmia, but this is less than the group A preponderance reported in addisonian anæmia[15]

TABLE I—BLOOD-GROUP DISTRIBUTION IN MEGALOBLASTIC ANÆMIA OF PREGNANCY

Blood group	Routine antenatal (3500 cases)	Megaloblastic anæmia of pregnancy			
		All grades (175 cases)	grade 3 (77 cases)	grade 2 (59 cases)	grade 1 (39 cases)
O	46%	43%	34%	48%	56%
A	42%	50%	60%	46%	36%
B	9%	5%	5%	3%	5%
AB	3%	2%	1%	3%	3%

When, however, cases of megaloblastic anæmia of pregnancy were classified according to their hæmatological grade (from 1 to 3), and the blood-group distribution calculated separately for each grade, it became obvious that there was only one category with a definite group-A preponderance—namely, grade 3—composed of those cases in which the marrow most closely resembles that of addisonian anæmia Table I shows that the incidence of blood-group A in 77 cases in category 3 is 60%, compared with a proportion of 42% in the controls As seen in table II, this difference is statistically significant ($P < 0 01$) On the other hand, the group-A incidence in those patients who were classified in grades 1 and 2 is 42%, which closely approaches the normal distribution

TABLE II—INCIDENCE OF GROUP-A IN MEGALOBLASTIC ANÆMIA OF PREGNANCY

Megaloblastic anæmia of pregnancy	Number of cases	Group A incidence	χ^2	P
All grades	175	50%	4 18	<0 05
Grade 3	77	60%	*9 16*	*<0 01*
Grade 2	59	46%	0 30	>0 5
Grade 1	39	36%	0 43	>0 5
Grades 1 and 2	98	42%	0 04	>0 5
Controls	3500	42%		

Analysis of clinical and hæmatological findings in women with the various grades of megaloblastic anæmia shows that grade-3 cases tend to present with more severe anæmia, higher serum-iron levels, and usually show a greater reticulocyte response to folic-acid therapy In other respects, patients in the various categories do not appear to differ Their age-distribution is similar and the incidence of achlorhydria is approximately the same A history of an inadequate diet in pregnancy appears with equal frequency in all categories, and the previous administration of iron does not seem to affect the marrow-picture Gastrointestinal symptoms, especially anorexia and ulceration of the mouth, occur equally often with lesser degrees of megaloblastosis

It would obviously be premature to draw definite conclusions from the blood-group distribution in a single series of cases from one district These findings suggest, however, that while folic-acid deficiency, with or without megaloblastic changes in the marrow, is a frequent occurrence in late pregnancy, patients with advanced megaloblastic anæmia constitute a special group in which there is an inherited predisposition to the disease The report by Giles and Burton[14] of 13 out of 41 cases of megaloblastic anæmia of pregnancy, with evidence of diminished fat absorption, has already pointed to a constitutional factor in the ætiology of the disease It is perhaps significant that a grade-3 type of marrow was found in 10 of these 13 cases

My thanks are due to Mr A H Iliffe, of the University College of North Staffordshire, for the statistical analysis, to Dr R B McConnell for his helpful advice, to Dr A J McCall for his help and encouragement, and to the research fund of the Birmingham Regional Hospital Board for its assistance

City General Hospital,
Stoke-on-Trent

C GILES
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[15] Fraser Roberts J A *Brit med Bull* 1959 15, 129

New Inventions

A HEART-LUNG MACHINE FOR INFANTS AND YOUNG CHILDREN

MOST heart-lung machines are designed for patients of 3 to 5 years and over Moreover, particular attention has been directed towards apparatus capable of maintaining the circulation in full-sized adults A number of congenital defects are responsible for death within the first year of life[1], but existing machines, with their relatively large priming volume, are not readily adaptable to the low flows and blood-volumes in this age-group

The following heart-lung circuit has been designed to provide flows up to 1 2 litres per min, with a priming volume of 500–750 ml

Apparatus

Basically this is a scaled-down version of the model in current clinical use[2] The oxygenator is of the rotating disc variety, and a heat-exchanger is included in the circuit The apparatus is entirely self-contained, being provided with its own source of heating and cooling fluids (see figure)

Two complete oxygenators are available (22 and 34 cm long) The smaller provides for flows up to 700 ml per min, and the larger for flows up to 1200 ml per min The discs are of stainless steel, 7 8 cm in diameter and spaced 4 mm apart Spacing of the discs at less than 4 mm causes foaming No silicone or anti-foam is required in the oxygenator The rotation speed of the discs is 120 r p m

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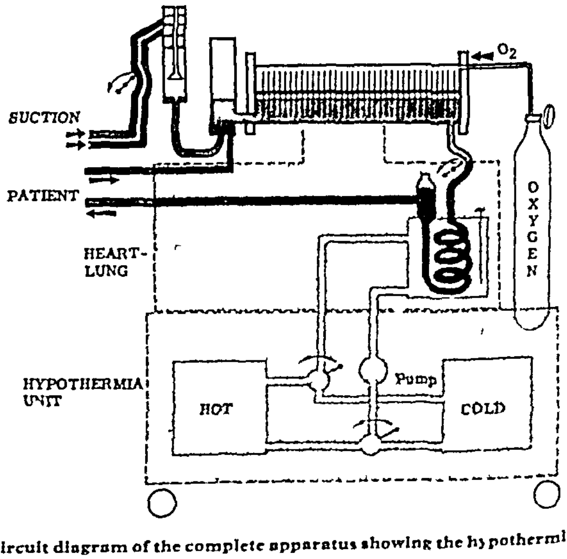
1 Bonham Carter, R E , Waterston, D J *Brit Heart J* 1957, 19, 589
2 Ross, D N *Brit med J* 1960, II, 571



Circuit diagram of the complete apparatus showing the hypothermia unit below

Cooling and rewarming is by means of a heat-exchanger constructed from stainless steel. A filter and bubble trap are incorporated in the arterial outflow line. Two sucker lines are provided which deliver their blood on to five perforated plates lightly coated with anti-foam. The output of the arterial pump and of the pump controlling the suction lines can be varied by two simple hand controls. The apparatus and tubing in contact with blood is sterilised in ethylene oxide for 24 hours before use.

The hypothermic and heating equipment is contained within a low trolley which acts as a mount for the heart-lung machine. In this way the apparatus, while remaining compact, is entirely self-contained. The cold source is supplied with a mixture of ice and water kept in a lagged 2 gal. tank, and hot water is kept thermostatically controlled at about 40°C in a separate tank.

Application

The apparatus has been used in twenty-five dog experiments. In addition, four children have been operated on, with one death. In use the machine requires very little adjustment, the running being in the hands of one technician.

The apparatus has been constructed for me by Mr. A. F. Turner in the Guy's Hospital Medical School workshop, and it will be available through Cardiac Recorders, Ltd., Weymouth Street, London, W.1.

Guy's Hospital,
London, S.E.1

D. N. ROSS
M.B., B.SC. Cape Town, F.R.C.S.

Reviews of Books

Medical and Dental Aspects of Fluoridation

W. A. CANNELL, M.R.C.S., D.P.H., L.D.S. London: Lewis. 1960. Pp. 125. 15*s*.

MOST of the growing literature of fluoridation and fluorine is scattered in various journals. A great deal of the research has been done in the United States, and the few books that have appeared since Roholm's classic text in 1937 have been published there. A British survey of the present state of knowledge is welcome, and Dr. Cannell gives a concise and readable summary, with an account of some important original work on the effect of trace elements.

It is a relief to find a book that deliberately does not discuss the various fluoridation trials in the United States. So much has been written about them and their real and alleged shortcomings that there is a risk of losing sight of one of the fundamental issues—the physiological and biochemical effects of fluorides. Too little is generally known about the systemic effects of fluorides, and Dr. Cannell's book should go a long way towards dispelling this ignorance, especially among the opponents of fluoridation.

The chapters on the pharmacology of the fluorides and on the calcification of skeletal and dental tissues are particularly good. Speculation is kept to a minimum, and the facts are presented fairly, and without bias. Not everyone will agree with Dr. Cannell in his excursion into the field of logical causality (p. 69), but the inescapability of fluorides renders his argument an attractive one.

The final chapter, on the public-health aspects, puts forward a well-reasoned case for the fluoridation of water-supplies. Other possible means of administration are discussed in the light of recent research. The bibliography is comprehensive and up to date, though there is no reference to Mackenzie's extensive review.[1]

This is probably one of the best accounts of fluorides and their effects that has been published for some time.

Pathology of Infancy and Childhood

AGNES R. MACGREGOR, M.D., F.R.C.P.E., F.R.C.O.G., reader in pathology, Edinburgh University. Edinburgh and London: E. & S. Livingstone. 1960. Pp. 631. 75*s*.

A VOLUME concerned entirely with pædiatric pathology has been urgently needed by many pathologists, and the gap has been partly filled by this book in which Dr. Macgregor incorporates the experience of her many years as an authority on this subject. It is a simple book: it makes no pretension to being a work of reference for pædiatric pathologists, but has been designed for the pathologist whose main work and interests are with older patients. Most conditions which he is likely to meet are considered adequately, with proper regard for their relative importance and incidence. Bearing in mind that the great majority of necropsies are on infants dying in the perinatal period, notes on necropsy technique and detailed practical accounts of perinatal conditions are included. Many facts in this part of the book rarely appear in print and are usually appreciated only after considerable experience. The section dealing with developmental anomalies could have been fortified by the inclusion of notes on embryology, supported by diagrams. Since many hospitals have cardiothoracic units, and deaths from cardiovascular anomalies often form a big part of pædiatric necropsy work, the account of these anomalies may be too superficial. Although the photographs of specimens of malformed hearts are generally self-explanatory, a few diagrams would have enhanced clarity. A lack of uniformity between different sections of the book is mainly due to the omission of conditions which are not peculiar to infants or children, or which are well described in standard textbooks of pathology. But a few relatively important diseases are treated rather briefly, and many less common conditions are not mentioned even by reference to the literature. Although the references are well chosen and up to date, the bibliography will be little help to the pathologist faced with an unusual case.

This book will be particularly useful to those embarking upon a career in pathology or pædiatrics. Its value to the established pathologist is limited, but it will be enjoyed by those who appreciate the signs of the author's wide experience.

The Chemical Senses in Health and Disease

H. KALMUS, SC.D., M.D., reader in biology, University of London; S. J. HUBBARD, B.SC., PH.D., lecturer in physiology, University College, London. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 95. 30*s*.

NO disciple of Brillat-Savarin needs to be reminded of the importance of the chemical senses—concerned as they are with taste and smell. But many may be surprised at the complexity of the physiological processes subserving the art of transcendental gastronomy. Who would have suspected, for instance, that over 60 volatile substances contribute to the aroma of coffee? This suggests almost endless permutation of naturally occurring odours and many kinds of odour-receptors. On the other hand, only four basic tastes—sour, salt, sweet, and bitter—are firmly established. The interplay of taste and smell, the importance of these chemical senses in behaviour both in animals and man, some curious and interesting genetical variations in both senses, and lines of future research and their practical importance are all discussed in this book. The psychological aspects—in some ways the most fascinating of any—are also briefly mentioned. The book is short and well worth the attention of physiologist and clinician. It is a pity the price is so high.

The Early History of Surgery

W. J. BISHOP, editor, *Medical History*. London: Robert Hale. 1960. Pp. 192. 18*s*.

AT a time when road travel is becoming increasingly dangerous, it is good to discover that some at least of its former hazards have been mitigated. Richard Wiseman, writing in 1676, described the misadventure which befell "a gentleman of about thirty years of age, who was coming out of Hertfordshire through Tottenham and riding upon the causeway near an inn when, one emptying a chamber pot out of the window

as he was passing by, his horse started and rushed violently between a signpost and a tree which supported part of the sign. The poor gentleman was beaten off his horse and lay stunned upon the ground." This case, and Wiseman's successful management of it, is one of the many which Mr Bishop uses to illustrate the evolution of surgery. His book is happily written in a style easily intelligible to the layman, yet technical enough to appeal to doctors as well, and, as might be expected from the author's status as an antiquarian, it is distinguished by a meticulous attention to accuracy. Even in such a matter as the emergency operation on King Edward VII, it is noted that it was never officially stated whether or not an appendicectomy had been performed.

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[1] Mackenzie, E. F. W. *Lancet*, 1952, i, 961.

The Healthy Child

His Physical, Psychological, and Social Development. Editors HAROLD C. STUART, M.D., emeritus professor of maternal and child health, Harvard University School of Public Health, DANE G. PRUGH, M.D., associate professor of pædiatrics and psychiatry, University of Rochester School of Medicine and Dentistry. Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1960. Pp. 507. 80s.

THIS book is written for all who work professionally with children, whether in the areas of medicine, education, social work, public health, nutrition, nursing, or psychology, and those who have contributed to it come from a correspondingly wide range of disciplines. The emphasis is on "healthy development" and how it may best be protected or promoted. The book presents in broad terms a picture of the child and his expected progress from conception to maturity. It is concerned with him as an individual who is changing or developing according to natural laws and inborn potentialities. It deals with the major aspects of his physical development and also with his psychosocial development and the factors which favour mental health. Among its many interesting chapters is one on emotional changes in pregnancy. Emphasising throughout the wide range of normal, the book is a valuable contribution to the increasing literature on the important subject of normality.

Life's Long Journey

KENNETH WALKER, F.R.C.S. London: Victor Gollancz. 1960. Pp. 191. 21s.

Mr Kenneth Walker writes, for the general public, to discount excessive claims for the material sciences in general, and in particular the supposition that natural selection sufficiently explains the course of human evolution and that scientific control could or should direct its future course, if any.

In the earlier chapters he seems to postulate "life" as a forward-looking entity planning its own development; but throughout the book "Nature", without inverted commas, appears as experimenter and giver or withholder of gifts, and it is not at all clear whom or what he regards as the "eternal mover", though he makes a firm claim for the life spiritual and the reality of mystical experience.

Like some others, Mr Walker regards the present population explosion as more dangerous to humanity than the atom bomb and fears our despairing recourse to Communist termitism. He is surely unjust to Ecclesiastes ("cast thy bread upon the waters") in ascribing to him and not to Proverbs the advice to look to the ant for exemplar, but that, in the present human predicament, the termitary is terrifying to contemplate is sure enough.

No Crying in this Cradle

The Expectant and Nursing Mother's Bedside Book. ELIZABETH G. MORRISON, S.R.N., S.C.M., M.T.S., JOAN GOLDMAN. London: Ernest Benn. 1960. Pp. 159. 15s.

Elizabeth Morrison has had a vast experience of reading and answering letters from mothers because for thirty years she has run the correspondence columns in *Nursery World*. But one wonders just how much practical experience she has had, and how recently. Some of the advice she gives is outdated—e.g., "it is advisable to go specially easy on meat in the last month or two of pregnancy." There seems little point in advising an expectant mother not to eat mixed grill and telling her that it won't make her or the baby "*feel too good*." The book says that eiderdowns for babies "ought to be forbidden by an Act of Parliament", not because they may smother the baby, but because "*nothing more effective exists to make the baby sweat*." Most of the book is an invective in favour of breast-feeding. But the reasons why babies should be breast-fed whenever possible are poorly argued and unconvincing. It is true that some doctors do not know much about normal babies, but it is doubtful whether many are as woefully ignorant as this book suggests. Doubtless dissatisfied patients write in sorrow and anger to the magazines, and Sister Morrison must receive many such letters. But to describe the doctor and baby clinic as "statistics-ridden prophets" who "yell the roof off with their denunciations" seems to be going rather far.

Nevertheless, the book contains a good deal of sensible, practical advice of the kind that is being given daily by good doctors and nurses up and down the country.

Clinical Bacteriology (2nd ed. London: Edward Arnold. 1960. Pp. 309. 30s.).—The duties of the bacteriologist in a hospital are to isolate pathogenic bacteria, to decide from collateral evidence and probability that these have some connection with the patient's illness, and—a recent development—to give guidance on the treatment of the infection to those responsible for the patient. The identity of the organism is not vastly important (except to the epidemiologist) but custom at least demands that this shall be reported as accurately as possible. It is this academic pride in going beyond the bare diagnosis and treatment which distinguishes the medical bacteriologist from the technician. When Dr Joan Stokes' book first appeared it was the best benchbook for the medical bacteriologist which had been published and it remains so today. The academic background (for which she still apologises) converts what might have been a mere cookery book into a readable and reliable guide to work at the bench. The changes in this second edition add some new methods and take account of some recent advances in knowledge, but as before it is clear that all the recommendations are made in the light of personal experience.

Demonstrations of Physical Signs in Clinical Surgery (13th ed. Bristol: John Wright. 1960. Pp. 928. 75s.).—In 1927 medical illustration was just emerging from the era of line drawings. Some textbooks contained a few photographs, but they were often reproduced in poorly contrasting shades of grey, and the technique of colour printing was in its infancy. When, therefore, in that year, the first edition of this book appeared, with its clear and vivid illustrations, students were quick to appreciate the efforts that Mr Hamilton Bailey and his publishers had made on their behalf. It comes as no surprise to learn that, of the English editions alone, 177,000 copies have now been sold. The latest edition contains more than four times as many pages and illustrations as the first, and if this growth-rate is maintained the twenty-fifth edition may well include *an illustration of the typical lesion* the volume produces by resting on the reader's knees. Many pictures have been furnished by distinguished clinicians, some of whom would no doubt acknowledge that they were helped to their first academic successes by the very work to which they have now contributed.

Principles of Orthopædic Surgery (London: J. & A. Churchill. 1960. Pp. 799. 150s.).—Dr Paul C. Colonna earlier published a book based on his lectures and teaching-rounds at the University of Pennsylvania. This volume is an expanded form (a notable difference is the increased space devoted to traumatic lesions) but has in common with the earlier one a style of writing and printing that makes for easy reading even over long periods. A few of the radiographs are not adequately reproduced, but the work is one of the very few which can be freely quoted on either side of the Atlantic without modification and with equal authority.

THE LANCET

LONDON 12 NOVEMBER 1960

Malaria Research

WHEN LAVERAN discovered the malaria parasite in 1880 he opened the flood gates to a torrent of research which, despite ebbs and flows, today runs as strongly as ever It seemed at various times that the problems of malaria had been finally solved at the end of the century when the mechanism of transmission through mosquitoes was worked out, the way seemed open (or so at least Ross thought) for the control and abolition of the disease, in the years between the wars, and later, a range of drugs was synthesised which seemed to offer the perfect therapy, then the researches on the exo-erythrocytic cycle from 1936 onwards had apparently filled the last gap in our knowledge of the life-cycle of the parasite, while the discovery of dicophane (D D T) and other residual insecticides was thought to have provided the final answer to the problem of mosquito eradication. And today, although we may feel that the end is in sight, this impression may be as false as any similar one expressed earlier in the century

The study of malaria involves so many disciplines that a special composite science—malariology—inevitably developed, with its own institutes, journals, techniques, jargon, and specially its cadre of international workers who have devoted their lives to this fascinating borderline of research The malariologist must be prepared to dabble in entomology and protozoology, in clinical medicine, in chemotherapy and biochemistry, in statistics and genetics, even in such uncongenial subjects as engineering, administration, and sociology An issue of the *Bulletin of the World Health Organisation*[1] illustrates something of this range. It includes a paper by SIR GORDON COVELL (who has been awarded the Walter Reed medal for services to tropical medicine) on the potential danger of apyrexial carriers of malaria in constituting an unobvious reservoir of infection during eradication campaigns, an account by A. S ALVING (Chicago) of a new method of administering primaquine (the drug which destroys the exo-erythrocytic stages of the malaria parasite and prevents relapses) by reducing the toxicity of this invaluable drug, a complete analysis by L T BRUCE-CHWATT and C GOCKEL, of W H.O, of the results of precipitin tests (carried out by B WEITZ, of the Lister Institute) of the stomach contents of anopheline mosquitoes, which showed that 48 out of 51 species fed to a greater or lesser extent on human blood, and other papers dealing with the action of dicophane and other residual insecticides R C MUIRHEAD-THOMSON, and G SACCA and Y GUY show how mosquitoes alter their habits after long exposure to dicophane—the so-called "behaviouristic resistance" The Colonial Pesticides Research Unit at Arusha suggests that the addition of a resin (ceredor) to gamma benzene hexachloride has provided the ideal insecticide for malaria control

Current research in malariology is as eclectic as ever Fundamental studies on the life-cycle of the parasite have been facilitated by using chimpanzees instead of volunteers, and BRAY[2] in Liberia, after finding that the liver of this ape is as susceptible as that of man to *Plasmodium vivax, ovale*, and *falciparum*, successfully demonstrated for the first time the tissue stages of the quartan parasite (*P malariæ*) by this technique There has been much controversy over the nature of nuclear division in malaria parasites, but BANO[3] has clearly demonstrated that the first division of the nucleus of the oocyst is meiotic, and that subsequent ones are mitotic, with a characteristic number of chromosomes in each of the seven species of plasmodia she studied The protective action of sickle-cell hæmoglobin against *P falciparum* was demonstrated by ALLISON[4] and other workers in 1954 and later More recently GILLES et al[5] have suggested that the possession of another hereditary trait—glucose-6-phosphate-dehydrogenase deficiency in red blood-cells—also has an inhibitory effect on the parasite.

Research on resistance has made much progress in the past few years In Algiers, SERGENT and PONCET[6] studied the development of resistance against chloroquine by *P berghei* in rats and mice, and introduced the term "mithridatism" for this feature The work of BISHOP[7] at the Molteno Institute went deeper and indicates that the resistance may have a mutational origin and be concerned with the metabolism of *p*-aminobenzoic acid and folic acid The resistance of several species of mosquitoes to insecticides presents a baffling problem in the eradication programme, and the genetic nature of this phenomenon has been shown at the Ross Institute, where DAVIDSON and JACKSON[8] demonstrated that resistance was of two independent types—to dicophane and dieldrin respectively, arising from single genetic factors, recessive in the former and semidominant in the latter, and applying to species of anopheline mosquitoes from as far apart as Africa, Indonesia, Iraq, and Central America This work has been confirmed to some extent by the cytological studies of FRIZZI and others[9] in Pavia, they have described in great detail the chromosome pattern of several species of mosquitoes, including susceptible and resistant forms These profound laboratory investigations stemmed directly from observations made in the field in Sokotu, Northern Nigeria, where RAMAKRISHNAN and ELLIOTT[10] noticed the sudden resistance to dieldrin of *Anopheles gambiæ* This is a good example of "incidental research", which has been a feature of malariology throughout its history

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[1] *Bull. Wld Hlth Org* 1960 22, no 6

[2] Bray, R. S *Brit med. J* 1959 ii 679

[3] Bano L. *Parasitology* 1959 49 559

[4] Allison A. C. *Brit med. J* 1954 i, 290

[5] Gilles, H. M. Watson-Williams, J, Taylor B S *Nature, Lond.* 1960, 185, 257

[6] Sergent, E. Poncet A. *Arch Inst Pasteur Algérie* 1959 37, 227

[7] Bishop, A. *Biol Rev* 1959 34, 445

[8] Davidson G, Jackson C. E. *Nature Lond* (in the press)

[9] D'Alessandro G Frizzi G, Mariani, M. *Bull. Wld Hlth Org* 1957 16, 859

Animal malaria, which has excited interest from the earliest days, has attracted fresh attention through the discovery[11] in the U S A that a strain of monkey malaria, isolated in London, readily infects man The parasite was named after G BASTIANELLI, the last of the great band of Italian malariologists, who died last year at the age of 96 This organism was being studied in three laboratories in the U S A, and, in all three, accidental infections occurred through the bites of infected mosquitoes The disease proved to be mild, and clinically and parasitologically resembled benign tertian malaria Subsequently G R COATNEY, D E EYLES, M E GETZ, and H K BEYE transmitted the infection back to monkeys and to volunteers, both by mosquitoes and by inoculation of blood containing parasites It was at once realised that here at last was direct evidence that monkeys might act as a reservoir of malaria in Nature, and that this infection might constitute a zoonosis Previously it had been well established[12] that another monkey parasite—*P knowlesi*—could easily affect man in its blood form, but mosquito transmission of this parasite to man has not yet been achieved, other simian parasites, such as *P malariæ* of chimpanzees and *P hylobati* of gibbons, are also suspected but not proved to be zoonoses *P cynomolgi bastianellii* (as this latest parasite is called) originated from a crab-eating monkey (*Macaca irus*) captured in Pahang, and the next stage of the research will be to discover first how many (if any) of the local inhabitants of this forested region are infected with the parasite, and secondly how widely it is distributed in the East Indies, Thailand, and the Far East With such a monkey reservoir of malaria, eradication may be an even more difficult undertaking than it seems at present, but, until the situation has been investigated fully, the extent of the danger cannot be assessed It may even be found that the parasite does not exist in Nature, but was the result of one of the flagrantly unnatural processes to which the parent strain had been subjected it was originally contaminated in both sexual and asexual forms with *P knowlesi*[13], it was flown across the Atlantic in iced blood, and it was maintained in a variety of exotic mosquitoes very different from its original insect vector

If malaria is to be eradicated from the world, these and other problems will have to be solved Even then the subject of malariology will not be extinguished, because much remains unknown about the malaria of lizards and birds, rats and lemurs, and bats and antelopes, and, though their parasites do not appear to affect man, the zoologist will be impelled to investigate them further, with their attendant insect hosts

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[10] Elliott R Ramakrishnan V *Nature Lond* 1956 177 532
[11] Eyles D E Coatney G R Getz M F *Science* 1960 131 1812
[12] Ciuca M Editura *Acad Rep pop Romine* 1955
[13] Hawking F Mellanby H Terry R J, Webber, W A F *Trans R Soc trop Med Hyg* 1957, 51 397

The Mongol Chromosome and Some Others

THE spate of new observations on human chromosome anomalies continues, and it seems worth following our recent attempt to survey the X chromosome disorders[1] with a similar account of one of the autosomes

Anomalies of the "mongol" chromosome (no 21 on the Denver system[2]) have been most studied indeed, apart from the sex chromosomes, this is the only one that can yet be associated in any but the most tentative way with a definite clinical syndrome Classical mongolism has now been shown beyond dispute to be caused by an extra chromosome, no 21[3-5] "Caused by", we would repeat though we do not know how the effect is produced, the relation is too strong to shelter behind the circumlocutory hedging implicit in the words "associated with" The production of "trisomy" of this kind, with three apparently normal chromosomes instead of the normal pair, by the process of non-disjunction during formation of the gamete, the effect of age on the incidence of non-disjunction, and the consequent explanation of the influence of maternal age on the incidence of mongolism are now familiar themes Interest is concentrating on certain cases in which the effect of trisomy-21 is produced by something other than the usual mechanism Such cases have been sought where youth of the mother, or (more certainly) evidence of familial transmission, has suggested that the ordinary non-disjunction mechanism has not been at work The first of these was reported by POLANI et al[6] earlier this year A mongol girl, one of a number examined because their mothers were much younger than usual at the time of their birth, was found to have the normal total number of 46 chromosomes One chromosome of the very characteristic medium-sized acrocentric group (nos 13–15, the "wishbones") was missing, and instead there was an atypical larger chromosome Ingeniously and most plausibly, POLANI et al accounted for this by assuming that the patient had a third no 21 present (thus accounting for her mongolism) but that this had fused with the missing no 14 (or thereabouts) to give the abnormal larger chromosome ("Fusion" oversimplifies the process, which is probably one of translocation, with exchange of material between two chromosomes if in this process a large fragment of one chromosome is exchanged for a small fragment of another, the result will be a large chromosome carrying most of the material of both and a small one carrying much less When these are separated in the process of gamete formation, imbalance will clearly result)

More recently PENROSE et al[7] have reported further "translocation" mongols One was much like the first, except that the extra no 21 was apparently joined to no 22 instead of no 14 In addition, they reported a most remarkable family Two mongol sibs each had 46 chromosomes, with the same 21/15 translocation-fusion to account for it In addition, three normal female relatives were found to have 45 chromosomes only In them an essentially normal chromosome complement had apparently been affected by the "fusion" of one chromosome each from the pairs 15 and 21 In this family the translocation had obviously occurred at least in the great-grandparents The mere joining together of two chromosomes had no recognisable effect, but the tendency to imbalance during gamete formation inseparable from this fusion gave rise to some offspring with too much chromosomal material, who were the mongols The importance of this form of transmission has been established by the description of a very similar but even larger family group by CARTER et al [8] The mechanism is fairly easy to follow from the diagram (fig 4) of POLANI et al [6]

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[1] *Lancet*, July 23 1960 p 191
[2] *ibid* 1960, i, 1063
[3] Lejeune J, Gautier, M, Turpin, R *C R Acad Sci, Paris* 1959, 248 602
[4] Jacobs P A Baikie A G, Court Brown, W M, Strong J A *Lancet*, 1959, i 710
[5] Böök, J A, Fraccaro, M Lindstern, J *Acta pædiat, Stockh*, 1959, 48 453
[6] Polani, P E Briggs J H Ford C E, Clarke C M, Berg J M *Lancet*, 1960, i, 721
[7] Penrose L S, Ellis, J R, Delhanty, J D A *ibid* Aug 20, 1960 p 409

Another remarkable family was reported by FRACCARO et al [9] Here the mongol patient had 46 chromosomes, and an abnormality of the smaller chromosomes which was thought at first to represent the ordinary mongol trisomy of no 21, with translocatory pseudo-fusion of two of the three to produce an abnormal single larger chromosome His father, who appeared perfectly normal and is a minister of religion (and who may thus be the first exception to the rule that chromosomal anomalies and university degrees are incompatible) was found to have 47 chromosomes and to be trisomic for no 19 The findings in this family admit of no simple explanation with our present knowledge, unless indeed (as seems unlikely) the diagnosis of the child as a mongol is at fault. But clearly we must expect some strange findings from the systematic examination of familial mongols There are rumours of yet other variants on the way

Anomalies of other chromosomes form a much more confusing picture. Trisomies of no 17 [10] and of one of the 13–15 group [11] seem well established Trisomy of no 22 is also not unlikely,[12] though identification of the chromosome present is not very certain (might it even have been an extra Y?) and its relation to the Sturge-Weber syndrome present cannot yet be accepted confidently Trisomy of no 11 [13] and of no 6 [14] have both been claimed, but both cases had the double sex chromatin characteristic of the XXX syndrome,[15–17] and, as we [1] and others [18] have already suggested for the first of these, these may well both be examples of the XXX syndrome with perhaps minor irregularities of one of the X chromosomes concerned Multiple trisomies have also been reported,[19 20] the most striking being FRACCARO et al's case [21] with 49 chromosomes altogether (nos 8 and 11 trisomic, plus XXY), and indeed, except for the viability of the patients, there is nothing incredible about this, for the conditions which cause non-disjunction of one chromosome pair could quite reasonably be supposed equally to affect others Perhaps the most nearly incredible of all the findings is the demonstration by BÖÖK and SANTESSON [22] of trisomy of every chromosome pair, giving a triploid individual with 69 chromosomes

It is too early to hope to decipher the pattern which must lie behind the varied clinical manifestations of these anomalies The sex-chromosome disorders present at least some trace of logic, and mongolism, though we have no glimmer of hint as to the mechanism by which the chromosome defect produces its highly specific effects, presents at least a consistent pattern Of the others hardly any two cases are sufficiently alike for conclusions to be possible It seems not unlikely that there will be found to be some non-specific tendency to congenital anomalies related more to the amount than to the nature of the chromosomal anomaly (mental defect being the most constant element), and a first task will be the identification, behind this screen, of more specific patterns related to disorders of individual chromosomes

The demonstration in viable children of triploidy [22] or trisomy of three large chromosomes [21] at one end of the scale, and in normal individuals of trisomy [9] or translocations [7 8] at the other, shows that the human organism is not as sensitive to such changes as was once supposed Every one of the twelve chromosome pairs of that old friend of the materia medica, *Datura stramonium*,[23] can exist in a trisomic form, and every one has its characteristic phenotype, or, as one calls it in medicine, its characteristic clinical syndrome Perhaps we will soon recognise equally characteristic syndromes for each of our own twenty-two autosome pairs

Tumours of the Bladder

IN the past decade the causes, treatment, and prevention of bladder tumours have aroused much interest. Fascinating questions surround the incidence of this disease Why is it increasing in younger males? Why is it apparently commoner in towns than in the country? Why is it rare in Japan and India? Now that β-naphthylamine is no longer employed in the dye, chemical, or rubber industry, which industries still use carcinogens such as benzidine?

A possible cause of bladder tumours is the excretion in the urine of an abnormal metabolite of tryptophane Some biochemists believe that this metabolite is hydroxykynurenin, others that it is hydroxyanthranilic acid or an allied compound These chemicals can be suppressed in at least three ways by administering pyridoxine, which alters tryptophane metabolism, or by administering saccharolactone, which inhibits enzyme activity in the urine, or by altering the urinary pH. Whether it will be possible by chemical means to prevent so-called "recurring" tumours, which may, in fact, be new tumours due to the persistence of a carcinogenic stimulus, depends on whether the mucosal changes are reversible or whether, once the mucosa has been stimulated by a chemical carcinogen, neoplasia is inevitable even if the stimulus is removed. Double-blind trials now in hand may provide the answer.

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[8] Carter C. O Hamerton J L. Polani P E. Gunalp A., Weller, S D V *ibid* Sept. 24 1960 p 678

[9] Fraccaro M. Kaijser K. Lindsten J *ibid* 1960 i, 724

[10] Edwards, J H. Harnden D G Cameron A. H., Crosse V M., Wolff, O H. *ibid.* p 787

[11] Patau, K. Smith D W, Therman, E. Inhorn S L., Wagner, H. P ibid. p 790

[12] Hayward M D Bower B D *ibid* Oct. 15 1960, p 844.

[13] De Carli L. Nuzzo F Chiarelli, B, Poli E. *ibid* July 16 1960 p 130

[14] Sandberg A. A. Crosswhite L. H., Gordy E. *J Amer med. Ass* 1960 174 221

[15] Jacobs, P A. Harnden D G Court-Brown W M., Goldstein J, Close H. G MacGregor, T N, Maclean N, Strong, J A. *Lancet*, 1960 i 1213

[16] Stewart J S S Sanderson A. *ibid* July 2 1960 p 21

[17] Fraser J Campbell J MacGillivray R. C., Boyd E. Lennox B *ibid* Sept. 17, 1960, p 626

[18] Jacobs, P A. Harnden, D G, Court-Brown, W M., Baikie, A. G *ibid* Aug 13, 1960 p 368

[19] Ford C. E., Jones, K. W Miller O J Mittwoch U, Penrose, L. S Ridler M. Shapiro A. *ibid* 1959 i 709

[20] Scandinavian cases cited by Fraccaro et al (footnote 21)

[21] Fraccaro M. Kaijser K. Lindsten J *Lancet*, Oct. 22, 1960 p 899

[22] Böök, J A., Santesson, B *ibid* 1960 i, 858

[23] Swanson C. P Cytology and Cytogenetics p 188 London 1958

In the treatment of the established case one adverse factor that can be attacked is delay. Patients often recognise hæmaturia as a symptom of possibly grave significance. But this view is not always shared by the patient's doctor, who may treat painless hæmaturia, without associated frequency or pain, as a case of cystitis, and when the bleeding stops the patient and his relatives are lulled into a false sense of security. In hospital, too, the possible gravity of the cause of hæmaturia is often not appreciated: recently a patient with this symptom was given an appointment to be seen in the outpatient department three months later. We accept pain in the right iliac fossa as a matter of urgency. Why cannot hæmaturia be given similar priority? In cases of carcinoma of the bladder, when the delay between the onset of hæmaturia and treatment is less than a month the 3-year-survival rate is 70.5%, but when the delay is 6 months the 3-year-survival rate drops to 36.8%.[1] Quick and accurate diagnosis is possible, and this is likelier to improve the results than any changes in the techniques of radical surgery or radiotherapy.

In the past ten years surgery and radiotherapy have each held sway in turn. Nowadays the limitations of surgery and the dangers of excessive radiotherapy are appreciated, the surgeon and radiotherapist work as a team, seeing, treating, and following up each case together. This makes for better results—for example, in cases treated surgically in which metastases develop and require irradiation, and in cases treated by radiotherapy in which surgery is needed for resultant complications.

Many factors, including the age and general condition of the patient, must be taken into account in treating bladder tumours. When the disease is localised and confined to the mucosa the choice lies between intensive diathermy (either cystoscopic or open) or some form of radiation. The complications of intracavitary radiation—contracted bladder, mucosal atrophy, and hæmorrhage—have led to its abandonment in such cases until better techniques can be evolved. Diathermy—either electrocoagulation or electroresection—is therefore the method of choice. The skilled surgeon can deal with even large tumours by this method, but this technique cannot be safely left to a junior. For limited tumours infiltrating no farther than the muscle coat interstitial irradiation may be applied. Formerly such tumours would have been treated by radon seeds, but nowadays artificially produced radioactive isotopes (gold or tantalum) are used. This represents a technical improvement, for radioactive gold grains are smaller, safer, more accurately implanted, and obtainable in various strengths, while tantalum is relatively cheap, has a much longer half-life than gold, and can be kept at hand so that after cystoscopy the bladder can be opened, the tumour excised, and wire implanted at a single operation.[2]

The supervoltage radiotherapy beam, directed either from generators, such as a linear accelerator or a Van de Graaf machine, or from artificially produced isotope bombs (telecobalt or telecæsium units), also has a place in treatment. This therapy can render a bladder tumour-free, but sometimes it completely fails to affect the tumour. Furthermore external radiotherapy in high dosage can produce radiation damage to the pelvic contents, including loops of small intestine. These risks, though small, must be weighed against the possibility of cure and the chance of conserving a normally functioning bladder. Using a linear accelerator at 8 MeV MORRISON[3] found that with a tumour dose totalling 4500–5500 rads in 4 weeks, 31% of patients had no tumour visible on follow-up cystoscopy. There was a better response with the earlier tumours (mucosal tumours disappeared completely in 43%, and a further 19% became appreciably smaller) but the more advanced tumours also regressed in many cases. These results show that supervoltage therapy is an extremely potent weapon and should be considered before recourse to radical surgery.

Partial cystectomy has tended to fall into disrepute, largely because it has been employed in the wrong type of case. MAGRI[4] has found that with single lesions, irrespective of the histological type (80% were solid anaplastic and infiltrating), where a clear margin of at least an inch was obtained there was a 71% 5-year-survival rate. Where, however, the line of excision cut through the tumour or its submucous extensions there were no survivors after 5 years. Partial cystectomy, though fairly easy, should be undertaken only after careful thought.

Radical surgery following radiotherapy is not difficult provided that irradiation has not been applied over too short a time to too large a volume of tissue or in excessive dosage. Radical cystectomy involves the removal of all the pelvic contents except the rectum, and also the lymph-nodes along the iliac vessels. WALLACE[5] has found that this operation, undertaken after radiotherapy, as the last weapon in the therapeutic armoury, carries a mortality of 21%, but that it can prolong life by 3 or more years in half the cases of mucosal tumours, a third of the cases in which muscle is infiltrated, and a quarter of the cases in which the perivesical fat has been invaded.

The treatment of bladder cancer is still far from satisfactory, but much can be done with our present resources to check the disease It is heartening to know that a subcommittee of the International Union against Cancer has agreed on a provisional method of classifying and reporting cases, similar to that adopted for cancer of the breast [6] If this recommendation is accepted the analysis of results should be greatly simplified

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[1] Report from the Institute of Urology and Southern Metropolitan Cancer Registry.

[2] Bloom, H. J. G. *Brit. J. Radiol.* 1960, 33, 171.

[3] Morrison, R. *Clin. Radiol.* 1960, 11, 125.

[4] Magri, J. Personal communication.

[5] Wallace, D. M. *Brit. J. Radiol.* 1960, 33, 187.

Annotations

POMP AND CIRCUMSTANCE

THE ceremonial ward round has long been a familiar feature of our teaching hospitals The Chief, surrounded by acolytes and disciples, proceeds in pomp from bed to bed, pausing now and then to correct a point of history, to confirm or deny the physical findings, to discuss the differential diagnosis, or to pontificate on methods of treatment. Ward-clerks and dressers stand around, shifting from foot to aching foot, bored registrars converse in whispers, nurses tiptoe past with bedpans, patients lie glum and silent while the Round drones on

Is this the best way of teaching " bedside " medicine and surgery? The *Oxford Medical School Gazette* [7] thinks not In a pungent editorial, entitled " Is Your W.R Really Necessary? ", the *Gazette* reminds us that such methods are frequently discourteous and may sometimes harm patients There the patient lies, sometimes half-naked, a forgotten object while the discussion rages over his bed He is listening, moreover, with apprehension to the list of alarming investigations proposed for him, to talk of frightful-sounding diseases that he might have, sometimes to obvious differences of opinion about treatment The more intelligent and educated he is, the worse his ordeal, for the more likely is he to glean from unguarded remarks some of the grimmer truths about his illness and to penetrate the thin veil of medical euphemisms It is easy to forget that nowadays, thanks to television and other media of mass information, many patients have a smattering of medical terminology and jargon And even if the Round removes itself a few beds away to discuss prognosis, other patients have ears, and ward gossip spreads The physical suffering imposed on ward-clerks by the peripatetic ward round is a less serious matter, but they might listen better and learn more if allowed to sit down comfortably

The *Oxford Medical School Gazette* suggests that all " bedside " teaching should take place in a room adjacent to the ward, with chairs, blackboard, and X-ray screen, into which patients can be brought when needed, or from which the Round can emerge for a brief visit to the bedside This sensible idea has already been adopted by some teaching hospitals We commend it to all Such an arrangement has the additional advantage of ensuring that the formal " round " is recognised as purely for teaching purposes, as it should be, and is not mixed up with the day-to-day management of patients It is impossible to teach properly on more than a few cases at a time Practical therapy should be dealt with by the Chief later, when he goes round his beds privately with his junior staff The traditional royal progress from bed to bed, with a gracious greeting and a few pearls of wisdom dropped at each one, may awe the impressionable but is not the best way either to teach clinical medicine or to cure patients

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[6] See *Lancet* 1959 ii 958
[7] *Oxf med Sch Gaz* 1960 12 41

NEONATAL RESPIRATORY DISTRESS

RESPIRATORY distress in the premature infant is a common cause of neonatal death Most of the affected infants have no evidence of congenital malformation or birth injury, hence they should survive if the distress could be prevented, and their recovery should be complete if it were more amenable to treatment The challenge to obstetricians (for prevention of prematurity is the best means of preventing these deaths) and to pædiatricians is being met, and there is some encouraging progress to report

In the past, research into respiratory distress has been largely concerned with the pulmonary and circulatory aspects [1] This has proved less enlightening than was hoped, for the ætiology of pulmonary hyaline membrane remains obscure,[2] and the reported disturbances in the mechanics of breathing do not add greatly to our understanding, nor do they suggest any sound alternatives to present methods of treatment based on the administration of oxygen and nursing the infant in a humid atmosphere

Interest has turned towards the biochemical changes associated with respiratory distress, and this may well prove a more productive approach The present position has been well summarised by James [3] Infants with birth asphyxia or respiratory distress become severely acidotic with hyperkalæmia, hypoglycæmia, and possibly hypocalcæmia These changes are the expected consequence of anoxia and retention of carbon dioxide They may well be responsible for death, and treatment with glucose, bicarbonate, and insulin holds out some promise of success [4]

The maintenance of a stable blood hydrogen-ion concentration (pH) depends on the lungs and on the kidneys, and the newborn baby is unique in both pulmonary and renal function [5] Some of the peculiarities of this period are now being elucidated Helen Reardon and her colleagues [6] have reported the results of a technically brilliant investigation into the chemical aspects of the control of respiration in the early newborn period They sampled blood not only from the umbilical vessels at birth but also from the temporal artery at various periods afterwards They analysed the blood samples for plasma pH, CO_2 content, protein, O_2 content and capacity, and hæmatocrit From these measurements the pCO_2, buffer base, and oxygen saturation were calculated The results showed that the normal full-term infant is born with mild acidosis which is of both metabolic and respiratory origin This is presumably due to an excess of fixed acids or deficiency of base which is uncompensated by hyperventilation The rise in pCO_2 (respiratory acidosis) suggests that the birth process not only prevents compensation of the metabolic acidosis but leads to impaired CO_2 elimination Within an hour of birth the respiratory component disappears owing to the efficacy of pulmonary ventilation, but the metabolic acidosis (decrease in bicarbonate or other buffer anions) tends to increase There is thus a state of uncompensated metabolic acidosis During the next few hours ventilation becomes efficient enough to compensate for the metabolic acidosis, and in some infants there is evidence of respiratory alkalosis Correction of, rather than compensation for, the metabolic acidosis takes place in breast-fed infants from the 4th day but is delayed in premature infants Reardon et al argue that plasma-pH is the main stimulus to respiration because, during the phase of compensating metabolic acidosis, there is still increased respiratory drive in the presence of lowered pCO_2 and plasma-pH

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[1] Cook C D Barrie H Avery M E *Advanc Pediat* 1960 11 11
[2] See *Lancet* Nov 5 1960 p 1014
[3] James, L S *Pediatrics* 1959 24 1069
[4] Usher R *ibid* p 562
[5] See *Lancet* 1960 i 583
[6] Reardon H S Baumann M L Haddad E J *J Pediat* 1960 57 151

McCance and Widdowson[7] have shown that the kidney of the newborn infant secretes an acid urine at birth and in the first 48 hours of life, the acidity is due not to acid phosphates but to a predominance of ammonium salts and organic acids, and Zweymuller[8] has identified some of these as emanating from the citric-acid cycle Probably, therefore, the newborn infant depends greatly on pulmonary function for the maintenance of acid-base balance, when this function fails the metabolic sequelæ may be catastrophic, and perhaps the biggest change is the hyperkalæmia Whether this hyperkalæmia is due predominantly to renal retention of potassium and excretion of sodium or to the excessive liberation of potassium from within cells is uncertain It seems reasonable, however, to attempt to prevent the extrusion of potassium from the cells by adequate oxygenation and administration of glucose

PRISONS IN 1959

LAST year, as the annual report of the Commissioners of Prisons[9] relates, the numbers of prisoners grew yet again (though it fell in the autumn), and the numbers of prison staff increased in rather higher proportion, although many more are still needed New legislation had a rather greater effect on the prison population than usual, with a drop of civil prisoners from 744 to 265 due to the Attachment of Earnings Order and an extra 63 prostitutes under the Street Offences Act Imprisonments without fine continued to rise (by over 2500 to 28,411 for men) as did receptions of men not under sentence (by 1000 to 45,000) This means, as the commissioners say, that a regrettably large proportion of the effort of local prison staff is diverted from training persons convicted of crime For women this defect is even more evident, for only 47% of those remanded before sentence were given imprisonment, and some 85% of these were imprisoned for not more than six months There is a widespread feeling that some alternative must be found to short prison sentences, and the new Criminal Justice Bill published last week (its terms are summarised on p 1082) may lead to their abolition at least for young offenders The suspended sentence was buried in 1952, and the Advisory Council on the Treatment of Offenders in 1957[10] did nothing to disinter it The Council did, however, approve adult attendance centres and call for wide use of remand on bail for full inquiry between conviction and sentence, believing that the knowledge gained in this way would help magistrates to avoid giving imprisonment Lord Kilmuir[11] offered detention centres as an alternative for under-21s—a group of prisoners which increased enormously in 1959 (by over 700 to 2498) Nevertheless, for men, sentences of under three months and over three years are tending to diminish slightly and intermediate ones to increase

Regarding types of offence, convictions for violence against the person again increased, though this may only reflect changes in public attitude and sentencing policy Gordon Hawkins[12] has described grounds for believing that in the past half-century violent crimes have not increased significantly Sexual offences continued their downward trend, but not those against females Thefts of all kinds again increased, but imprisonment for drunkenness decreased (by about 200 to 3129) Heavy traffic and current anxieties about road deaths were doubtless partly responsible for the great increase in imprisonment under the Highway Acts—at 2627 the total last year was nearly 50% greater than in 1958 The views of Lady Wootton[13] and others are evidently making some impact on her fellow magistrates (Even so, the Royal Automobile Club[14] has pointed out that, while all traffic offences increased by 6 6% in the year, traffic volume went up by 10%) Local prisons, unfortunately, still carry the greatest load, holding about 4 prisoners to every 1 accommodated elsewhere Clearly "show" prisons such as Wakefield tell but a small part of the story

Breaches of discipline and escapes continued to cause concern Birching was ordered 11 times (3 in 1958), and this punishment was confirmed in 2 cases by the Home Secretary (0 in 1958) That 1 of these 2 men committed a second assault shortly afterwards must reinforce the belief that the value of corporal punishment is mainly to assuage the feelings of the staff In the contrary direction, however, the approach towards a "therapeutic community" proceeds The Norwich system of freer association between staff and prisoners continued to expand, and group counselling[15] spread to fourteen more prisons and borstals in the year Even at Dartmoor, this system has had a good reception Evening classes are expanding, but progress towards the realistic full-time work and reward system, so essential in training a man for ordinary life, is still disappointingly slow Nevertheless, an Advisory Council on the Employment of Prisoners has been set up, together with a new post of assistant commissioner (industrial) It is one of the anachronisms of the age that thousands of able-bodied men moulder away in gaols while public works, such as waterways and the decaying relics of the 1939–45 war, lie neglected But at least the pre-release hostel and training scheme is spreading as its success becomes more obvious Another means of reintegrating the offender with society is by home leave, over 300 borstal lads were thus paroled, and only 1 in 30 broke it

Detention centres remain one of the brighter hopes of the commissioners for coping with the "bulge" of moderately delinquent youth, and the new Bill seeks to make wider use of these centres But, despite great shortage of places, unsuitable lads—persistent offenders, the physically or emotionally disturbed, and approved-school failures—are too often sent to these centres, where they are not helped by the brief period of highly disciplined and energetic life, and where their presence has an adverse effect on others A better system of classification or of advice to magistrates is needed Whether this stern type of institution is more effective than milder methods has still to be shown by valid comparative techniques Over 50% of boys discharged in 1956 and 1957 had been reconvicted by 1960, and this does not sound too hopeful Aftercare, as the commissioners sadly note, is not yet compulsory, but the new Bill includes provisions for its extension to those coming out of detention centres

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[7] McCance, R A Widdowson E M *Acta pædiat, Stockh* 1960, 49, 409

[8] Zweymuller, E *ibid* p 591

[9] Report of the Commissioners of Prisons for the Year 1959 Cmnd 1117 H M Stationery Office Pp 199 9s 6d

[10] Alternatives to Short Terms of Imprisonment H M Stationery Office, 1957

[11] *Times*, Aug 9 1960

[12] *Criminal Law Review* October, 1960

[13] Wootton B Social Science and Social Pathology London, 1959 See *Lancet* 1960, i, 1238

[14] *Times*, Aug 10, 1960

[15] See *Lancet*, 1959, ii, 1015

Physical health in prisons remains good, and the trend towards using outside facilities continues, but the number found insane on remand jumped to almost double despite a decline in the number remanded for mental observation and report It is hard to explain these trends, perhaps the new outlook inherent in the Mental Health Act of 1959 may have permeated the prison medical services more quickly than it has influenced the judicial authorities

The prison services, avowedly therapeutic organisations these days, are under as much obligation as, say, the manufacturers of drugs to assess and to publish their results, particularly where new techniques such as group counselling are introduced In a recent lecture the Home Secretary [16] endorsed the views on research we put forward last year [15] It is therefore disappointing to find so little about new methods in the report In support of group counselling it includes a few staff impressions and a couple of letters from prisoners, only in an appendix is there some worth-while evidence—from a local prison where, despite a rising population, the Norwich system led to a drop in disciplinary reports of 131 to 369, and the continuing lapses were less serious than before Other than this, the cynic might be led to correlate the trend towards easier relationships in and out of the prison with the increase of indiscipline, escapes, and overcrowding which the report mentions A larger chapter on "Research" is needed in this valuable document The Home Office research unit, which is already doing a great deal, should stop hiding its light under a bushel Bricks and mortar may still be badly needed, but knowledge must be given a new priority

HUMORAL AGENT IN MIGRAINE?

BROADLY speaking, the mechanism by which symptoms are produced in an attack of migraine is agreed, but the exact changes in cranial blood-vessels and nearby structures which cause the characteristic head pains are still in dispute

Chapman et al [17] working on the hypothesis that besides local vascular change some inflammatory or pain-producing substance was produced locally, examined tissue-fluid from regions of the head which were tender during a migraine attack Specimens were collected by slowly injecting 2 ml of sterile physiological saline solution into the local subcutaneous tissue and then gently withdrawing some of it Controls were provided by taking samples from the scalps of migraine patients both during attacks and at other times, from people not subject to headache attacks, and from the subcutaneous tissue of the forearms of each subject In the headache subjects a substance was found which bioassay suggested was a polypeptide This substance, for which Chapman et al suggest the name "neurokinin", was present in small quantities in all specimens from all subjects, but very much larger quantities were found in tissue-fluid from the scalp of patients with headaches at the time the specimens were taken It was also found to be released into the segmental cutaneous tissue-fluid during dorsal root stimulation and in the axon flare reaction In one subject the substance was apparently reduced in amount after administration of ergotamine tartrate, and Chapman et al suggest that interference by ergotamine with an enzyme system liberating "neurokinin" from a plasma-globulin may be the basis of this effect

These results are extremely interesting They may possibly explain some of the longer-lasting features of migraine which apparently outlast the aura and headache But bioassay methods can be unreliable, and these findings will need to be confirmed and the substances if possible defined chemically

TUBERCULOSIS IN AFRICA

IN the first of the four Heath Clark lectures, delivered in London on Nov 2, Dr Charles Wilcocks traced the development of investigations into tuberculosis in Africa This disease, he said is still spreading, and drug treatment by itself is unlikely to provide the whole answer

Wide variations in incidence and mortality among different races, noted as long ago as the beginning of the century, had led Cummins to formulate his "virgin soil" theory According to this, primitive tribes were highly susceptible because, in the absence of the bacillus, they had never in their own surroundings been obliged to protect themselves against it, while those living in more urban communities had elaborated protective substances through contact with the bacillus The high tuberculosis incidence and mortality among African troops in Europe in the 1914–18 war seemed to support this theory, though subsequent workers had suggested that the troops involved had been in France for some time and that they broke down under stress in other words, that the cause lay more in the environment than in racial susceptibility

Between the wars extensive work by individuals and commissions, ably supported by administrators, led to an accurate assessment of the distribution and character of the disease It was found to be widely distributed and it progressed rapidly to death, with extensive cavitation and little fibrosis, and usually with involvement of both lungs The sputum was heavily infected, and this was clearly a factor in spread when the patient and the rest of his family slept together in small, poorly ventilated houses

Some idea of the distribution of the disease could be gained from the large proportion—41%—of the total health expenditure of the Union of South Africa devoted to tuberculosis In the mines pneumoconiosis had added to the problem, although more careful selection of recruits and measures to cut down dust had reduced the number affected

Treatment, previously limited to bed rest and an occasional pneumothorax, had been radically changed by the advent of effective drugs But these might fail to control the disease, especially if the patient was not treated in hospital, because many did not take *p*-aminosalicylic acid with their isoniazid, and others stopped treatment before they should Thus resistance developed on a large scale

B C G vaccination was sometimes the only rapidly applicable preventive measure, and its value was probably small But these were short-time measures For widespread improvement, the attitudes of members of very different cultures had to be modified and research undertaken into the means of persuading whole communities to change habits which favoured the development of tuberculosis The most pressing need was improvement in environmental conditions The emphasis had now shifted to stress as the main causal factor in tuberculosis Nutrition, housing, working conditions, and hygiene and sanitation all required attention The £10 million per annum spent by the South African Government in the past five years on housing for non-Europeans was a step in the right direction It was unfortunate that the World Health Organisation, in its last report on the subject, had barely touched on the environmental factor, presumably because it was considered self-evident But anything which was not mentioned tended to be forgotten

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[16] Penal Reform and Research By R A BUTLER Liverpool University Press 1960 Pp 14 3*s* 6*d*

[17] Chapman L F, Ramos A O, Goodell H, Silverman, J, Wolff, H G *Arch Neurol* 1960, 3 223

It was the doctor's duty to stimulate the administrators to improve conditions, just as had been done in England a century ago

A SEX-LINKED FAMILIAL PURPURA

THE classical sex-linked hereditary bleeding diseases are hæmophilia and its close relation, Christmas disease In the past six years there have been reports of a purpuric hæmorrhagic disorder with a similar mode of inheritance by a sex-linked recessive gene—i e , the condition affects males but is transmitted by female carriers who are unaffected, and each male has an equal chance of being affected or free The condition, first described in 1954 by Aldrich et al ,[1] presents the odd combination of thrombocytopenic purpura, eczema, and undue liability to infection In the family, of Dutch extraction, observed by Aldrich et al , the male infants were known to be liable to die in the first few years of life with " draining ears, eczematoid dermatitis, and bloody diarrhœa ", in the last three generations 16 out of 40 males had died with this disease before the age of 31 months Krivit and Good [2] investigated the same family in 1959 and found that there were 2 female carriers who were reproducing, and that these had had 8 children since 1954, 2 were healthy girls and 6 were boys, of whom 3 had the disease and 3 were healthy

2 cases in an English family have now been reported by Gordon,[3] of Sheffield He points out that seven families affected by the disease have been described, one of them a Negro family Details of 16 male patients are known, and all have died, 1 of Gordon's patients has died, and 1 is still alive

Gordon's 1st patient was admitted to hospital at the age of 14 months with infantile eczema affecting the head, neck, arms, and legs A bleeding tendency had been noted from the age of 4 months, and this had alarmed the mother because she had had a brother who had died of " hæmophilia " at the age of 1 year Investigation showed severe thrombocytopenia, which persisted except for short periods when the count rose above 100,000 per c mm Bone-marrow was found to contain platelet-forming megakaryocytes With treatment the eczema improved, and the patient was sent home He was in hospital again on account of eczema five months later, and at the age of 4 years he was admitted with profuse purpura, bleeding gums, discharging ears, and impetigo The thrombocytopenia being still present, it was decided to carry out splenectomy, and this was followed by a rise of platelets to normal and disappearance of the purpura But in the next twelve months the patient had to be admitted three times—once because he had meningitis due to pneumococcal and staphylococcal infections, once for dental extraction which caused no trouble, and finally in a fatal coma Necropsy showed bilateral adrenal hæmorrhages, there was no evidence of septicæmia, the platelet-count was not recorded

Gordon's 2nd case was the brother of his 1st patient, born eight years later, in between, a healthy girl and a healthy boy had been born This 4th child of the family showed eczema at the age of 3 months, and a month later he was investigated in hospital, he had thrombocytopenia, and furunculosis, pyuria, and bronchitis developed while he was in hospital His white-blood-cell count was normal, and he did not have deficient γ-globulin Treatment with prednisolone and then with corticotrophin produced only a temporary rise in the platelet-count In view of the experience with the elder boy splenectomy was not performed, and the patient has remained reasonably well for three years, still having occasional purpura and occasional attacks of respiratory-tract infection

This syndrome will be easily recognised, though we have no doubt that children with eczema and thrombocytopenic purpura will be seen who do not have the syndrome, the added features of recurrent infection and, above all, a positive family history must also be found The cases so far reported have not been very fully investigated Krivet and Good sought platelet agglutinins but did not find them, marrow punctures have shown the same picture as that of " idiopathic " thrombocytopenic purpura, γ-globulins appear normal But nothing is known about the other blood-clotting factors No attempt seems to have been made to find out whether the condition is linked in any way with systemic lupus erythematosus and similar diseases, in which thrombocytopenic purpura is sometimes an early sign We hope that pædiatricians will look out for cases of Aldrich's syndrome and see whether more can be learnt about its ætiology and possible lines of treatment

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[1] Aldrich R A Steinberg A G , Campbell, D C *Pediatrics* 1954, 13 133

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CHEMICAL MENINGITIS
FOLLOWING SPINAL ANÆSTHESIA

FORMERLY, when measures were not taken to avoid contamination of the subarachnoid space with phenolic disinfectants, chemical meningitis was a recognised sequel of spinal anæsthesia [1] Sterilisation by autoclaving of special packs containing all the equipment, including the ampoules of local anæsthetic, required for this form of anæsthesia is now commonly practised to prevent this complication But autoclaving by itself is inadequate if the syringes and needles have not been previously freed from all traces of disinfectant by cleansing and washing

The dangers of inadequate washing of equipment are well brought out in an account of five patients in whom acute meningitis developed very shortly after spinal anæsthesia for obstetric delivery [2] The cerebrospinal fluid in each case was purulent, with a polymorph leucocytosis These findings, together with pyrexia, suggested bacterial infection of the subarachnoid space, but no organisms could be isolated from the cerebrospinal fluid or from blood samples A review of the procedures used for cleansing spinal anæsthetic equipment in the obstetric department concerned revealed that, whereas the ampoules of local anæsthetic were taken directly from their carton before autoclaving, the syringes used were soaked in a solution of a phenolic disinfectant, washed and rinsed, and finally put in trays ready for autoclaving Clearly this washing was ineffective Fortunately, all five patients recovered without permanent neurological sequelæ Their illnesses illustrate once again the dangers associated with this mode of anæsthesia when insufficient precautions are taken to avoid contamination of the subarachnoid space

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[2] Goldman W W Sanford J P *Amer J Med* 1960, 29 94

Points of View

FUTURE ROLE OF THE FAMILY DOCTOR*

E MAURICE BACKETT
M B , B Sc Lond , M R C.P , F S S , D P H
PROFESSOR OF SOCIAL MEDICINE IN THE UNIVERSITY OF ABERDEEN

WITH the changing patterns of disease in Western societies, particularly the emergence of the chronic diseases (heart-disease, cancer, peptic ulcer, bronchitis), of accidents (especially motor-vehicle accidents), and of the multiple effects of radiation as the characteristic and newly important threats to the public health, there has come the possibility of a rather different sort of medical care This new approach is preventive in attitude (though the borderline between prevention and very early treatment is rapidly becoming meaningless) It is preventive in the sense of using our growing epidemiological knowledge accurately to define vulnerable groups, families, and individuals in our population and of manipulating their personal and social environment to prevent disease But the differences between the present and future preventive medicine are more important than they seem at first sight These days (and at long last) most of us accept the necessity for clean milk and the quality control of food, for example, without demur These controls are, for the most part, satisfyingly impersonal But just let us try advocating changes in the individual and family dietary customs of the healthy rather than the sick in our practices, or their leisure pursuits, or try to change one of many minor addictions to which we are all prone, and we are in for trouble That trouble is made subtly worse by a sneaking feeling that we may have no right to meddle in these personal matters anyway, and that our techniques, if we do, are naïve Yet, if the future general practitioner is to attempt the control of chronic disease in his practice, he has little choice—he *must* meddle, and his meddling must be increasingly personal, for it seems very likely that before long our so-called " new " diseases will offer as much of a threat to life and happiness as did some of the epidemics of the 19th century And, since many of these diseases have their origins in our changing ways of living, a tolerable amount of interference may help to prevent them

By " new " diseases I do not mean only novelties but *newly important* diseases which, because of their increasing contribution to our morbidity and mortality, must be counted as new threats For example, with the decline (but not the defeat) of the infections we can see more clearly the enormity of our chronic-bronchitis problem (25 million man-days lost per year, and thousands of deaths), of our cancer problem (100,000 deaths per year), of heart-disease, and of chronic but not always fatal diseases like diabetes and multiple sclerosis We see, too, the useless (though fortunately small) waste of fœtal and neonatal life and the few remaining maternal deaths in a new context the context of a society which, perhaps unlike all previous societies, does not expect illness and early death and which thinks of health and happiness as its right

* * *

We can summarise the main features of our changing disease patterns in this way First, the *vulnerable age-groups* are shifting Young people are seldom ill In fact the older children and adolescents have virtually disappeared from the doctor's surgery There is increasing emphasis on the intrauterine child and the neonate, rather than the infant Then there is the new interest, of course, in the elderly, and above all a growing anxiety about the middle-aged The *sex ratios*, too, are changing, and the new diseases are increasingly selective of males

Next, the *type of disease* is changing (and, inevitably, our attitude towards it) For example, infectious disease outbreaks are often spectacular and explosive, cases occur near one another, a hundred or so deaths in a small community has the impact of disaster, while the same number of deaths spread over the whole country—motor-vehicle or coronary deaths, for example—does not carry the same provocative danger signal Some catastrophe is needed to promote social action

Next there is the *duration of illness* Most of our new diseases are chronic slow-moving processes which may take many symptomless years to develop We are told that the cancer of the lung, for example, may have started fifteen or twenty comparatively healthy years before the first symptom of the disease, and that the men now dying of chronic bronchitis may well be reflecting not only their smoking habits and the air pollution of the cities in which they have lived but also the shorter convalescence enforced on working-class families by the tough economic pressures of the hungry '30s It is, perhaps, this very long duration of our chronic diseases and of cancer which is doing most to force us to review our methods of medical care

Finally, we can say that with a few exceptions our new threats to health seem, by their very nature, somewhat less likely to respond to curative medicine than the diseases of the past However, this point is not a strong one, and, to strengthen the case for a review of our preventive measures, I would say that, thanks to the impeccable epidemiology of people like Doll, Case, and Morris, the prevention of many cancers (and some other chronic diseases) is becoming possible long before the disease itself is fully understood Thus, in the face of our new diseases, *prevention* acquires a new urgency, and the wise family doctor is being forced increasingly to switch his attention from sick people to the habits and behaviour of healthy people many years before the clinical onset of illness

* * *

So here, very crudely, is the problem Most people who feel ill seek medical care and have a rather special relationship with their doctors Healthy people, on the other hand, are unlikely to be particularly impressed by talk of a disease which *may* come in twenty years' time Their replies to doctors who seek to change their behaviour, and thus to promote their future health, are polite but negative

The dilemma is most acute for the family doctor, for it is now becoming technically possible for a large part of his job to be the highly scientific supervision of healthy people Indeed, this looks like being the only way to cope with our new diseases Such a statement does not sound particularly surprising, but at the moment well over 90% of the family doctor's work with adults is curative, dealing with established disease If even a quarter of his work were to be concerned mainly with healthy people, rather than the sick, this would be a revolutionary change—at least as revolutionary as was his assumption of the role of vaccinator and immuniser of children Such a change has been made *necessary* by the changes in our disease pattern, and *possible* by a growing knowledge of the reasons for variation in the vulnerability of different age, sex, and social groups This means that the doctor who really knows how his patients live will be able to define with increasing accuracy who is likely to become ill In fact, he alone—because of his contact with the family—can become the man to observe those aspects of behaviour which we suspect are the precursors of much chronic disease

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* Abridged from a paper read to the sociological section of the British Association on Sept 2, 1960 The full text will appear in *Advancement of Science*

As a help toward the practical application of this change of approach, the doctor now has a growing armoury of screening devices and simple tests by which he can pick the already ill from among the merely vulnerable people in his practice, and so make earlier and ever earlier diagnoses Many of these screening tests are sensitive enough to be used while the patient is still feeling fit—that is before he would normally seek medical care, and long before serious symptoms arise

* * *

These notions may be illustrated briefly by reference to cancer of the uterine cervix Epidemiologically speaking, this cancer is well described A lot is known about what sort of people get it (but, of course, very little about how they get it) Through relatively simple technical advances it is becoming possible to make increasingly early diagnoses of the developing growth We are told that treatment at an early stage is relatively easy and safe, but that the diagnosis must be made before the symptoms and signs develop We are also told that the test is rapidly achieving real accuracy So it is this combination of good epidemiology (which could guide the doctor to where the disease will arise—so that he need not screen all the women in his practice) and this early test which has suddenly given the family doctor the power if not to eradicate the disease then perhaps drastically to reduce it in his practice But, at once we are back with the same problems as before How to persuade apparently healthy women who belong to the vulnerable age, parity, and social group to seek medical care long before they feel ill, how to persuade the doctor to persuade them, and finally, how to fit this approach into a service and a society quite naturally preoccupied with curative medicine

* * *

Tests which can be used for screening apparently healthy populations for all manner of different diseases are rapidly increasing in number and accuracy They are an exciting product of the growing gadgetry of medicine Already it seems probable that more or less accurate and very early diagnoses (that is, long before the patient is conscious of illness) can be made in a variety of chest conditions, a few cardiovascular disorders, some renal diseases, and an assortment of hereditary metabolic upsets, mild diabetes, and at least one cause of blindness

In this way it seems that our new diseases are themselves forcing us into at least the contemplation of a different sort of medical care This medical care may in turn need a rather different sort of doctor to apply it Such a man would have different interests and would need much more time than today's family doctors whose hospital education very properly emphasises curative medicine above all else

There are other difficulties apart from those of time and interest For example, most doctors feel that, at least at first, we should play a passive waiting role the initiative obviously should be with the patient With this in mind most of us would find it very difficult, for example, to write to a lot of healthy adults on our lists *inviting* them to undergo even the simplest of screening tests It would be even more difficult to go to the length of reorganising our practices so that much of our time was spent in this way

There is yet another problem How could the future family doctor screen the vulnerable people on his list, offer his genetic counsel, advise effectively on diet, exercise, and so on, or even check the blood-pressure and weight of the paunchily middle-aged (if one day it is agreed that these too are useful screening tests) without creating not a healthy practice but a practice of neurotics? We have seen a suggestion of this mass fear of illness following the indiscriminate " check-up " campaigns, the cancer films, and the commercial exploitation of anxiety which has occasionally been a feature of " health education " elsewhere Our small experience of studies over here, and the wider experience of calmly and well run studies of community health (such as that at Framingham in the U S A), suggest that these dangers can be avoided But they remain an important threat, and the prevention of some heart-disease, for example, might save the lives of mentally healthy men at the cost of converting them into cardiac neurotics

* * *

Changes in disease patterns must always have given rise to new social problems our current transition from the infections to chronic degenerative disease is obviously no exception The changing role of the general practitioner is among the most intriguing of these problems, and it may be that in future he will have to be prepared to make himself more of a nuisance to his patients But if he does, will they take any notice of him—and why should they anyway?

Public Health

Infectious Diseases in England and Wales

Disease	Week ended October				
	1	8	15	22	29*
Diphtheria	4	3	4	4	
Dysentery	477	500	600	465	581
Encephalitis					
Infective	1	3	4	2	3
Postinfectious	3		2	2	
Food poisoning	287	225	188	181	196
Measles excluding rubella	996	2856	3220	3917	4585
Meningococcal infection	19	28	29	19	18
Ophthalmia neonatorum	24	16	24	31	9
Paratyphoid fever	6	7	12	4	7
Pneumonia primary or influenzal	175	202	239	213	221
Poliomyelitis					
Paralytic	12	14	8	10	13
Non paralytic	6	4	7	1	2
Puerperal pyrexia	153	194	201	188	171
Scarlet fever	305	357	424	465	409
Smallpox					
Tuberculosis					
Respiratory	387	386	428	436	343
Meninges and C.N.S	2	2	2	2	6
Other	48	44	47	57	51
Typhoid fever	5	4	1		3
Whooping cough	1110	1024	934	860	964

* Not including late returns

Special Articles

EAST-WEST SYMPOSIUM ON PATHOGENESIS OF ESSENTIAL HYPERTENSION*

CLIFFORD WILSON
D M Oxon., F.R.C.P
PROFESSOR OF MEDICINE, UNIVERSITY OF LONDON,
DIRECTOR OF THE MEDICAL UNIT, THE LONDON HOSPITAL, E.1

"ALTHOUGH it appears that essential hypertension is a widespread condition and a frequent cause of premature invalidism and death, there is little agreement about its pathogenesis or about the role of various environmental factors in its production. This lack of knowledge prohibits any rational attempt at prevention It seems desirable, therefore, to discuss the conflicting views and to delineate fields in which future research might possibly be concentrated with profit."

These were the broad terms of reference of a symposium which was held in Prague early in the summer under the joint auspices of the European Region of W H O and the Czechoslovak Cardiological Society Some 40 workers, engaged in research on various aspects of hypertension, attended, chiefly from the U S.A , U S S R , and Great Britain, but almost every other country in Europe was represented

The detailed proceedings of the conference will be published shortly, and these will include an account of individual papers and the variety of opinions expressed in discussion Nevertheless it seems worth while to record some personal impressions now which it is hoped may give some idea of the positive achievements of the symposium Research on hypertension has recently received a fresh stimulus from several different directions, and this was reflected in the lively controversy and some new ideas which found expression during the symposium

One stimulus in Prague was undoubtedly the opportunity of hearing from Russian investigators about their concept of essential hypertension as a specific neurosis, against the experimental background of hypertension induced in animals by nervous or emotional strain New interest has also been aroused by epidemiological studies on the role of genetic and environmental factors, one outcome of which is the current controversy on whether essential hypertension is a disease entity or a biological variation differing only quantitatively from the normal Furthermore, the widespread use of hypotensive drugs with a variety of pharmacological effects has not only emphasised the need for a clearer understanding of the fundamental nature of the disorder, but has also produced some new ideas about possible mechanisms in its pathogenesis In the investigation of these problems, statisticians, physiologists, experimental pathologists, and pharmacologists are becoming increasingly active The old controversies about humoral and neurogenic mechanisms have been given a new look by the discovery of intriguing relationships between renin and aldosterone, by more critical assessment of the role of catechol amines, and by the researches of neurophysiologists in several countries on the nervous regulation of the circulation. Added to this is a questioning of the old concepts of the hæmodynamic status in hypertension in which circulatory changes were accepted as incidental to a primary increase in peripheral resistance, so that the search for ætiological factors was focused almost exclusively on this restricted part of the vascular system

The symposium was arranged as a series of discussions on the following topics definition, diagnosis, and natural history, epidemiology, the role of emotional and environmental factors, neurogenic factors in the control of blood-pressure, hæmodynamic studies in essential hypertension, vessel-wall factors, metabolic factors, including the possible role of pressor amines, the adrenal cortex, and the kidney

Although there was considerable divergence of opinion on most of the topics discussed, there was a fair amount of agreement on the nature of the problems which need to be tackled These I have attempted to summarise in the following questions

(1) In the light of modern knowledge, can we arrive at any more satisfactory definition of essential hypertension than the present one of "elevation of the blood-pressure without apparent cause"?

(2) In view of the more exact methods of diagnosis now available, how large a proportion of cases, masquerading under the diagnosis of essential hypertension, are really due to some local disease—e g , of the kidneys or endocrine glands?

(3) Is it possible to find a means of separating normal from high blood-pressure, not only in the numerical sense, but also in establishing whether essential hypertension is qualitatively different from the physiological range of the blood-pressure?

(4) How valid are casual blood-pressure readings, especially when used as an index in epidemiological studies? How far can such blood-pressure readings be standardised?

(5) How large a part does heredity play in the pathogenesis of essential hypertension? Is the genetic factor sufficiently large to indicate a primary metabolic fault in blood-pressure regulation as the main cause?

(6) What is the role of environmental factors such as geographical situation, diet (including electrolyte intake), occupation, and particularly, mental strain or emotional stress?

(7) Does the blood-pressure rise with age uniformly in the population as a whole, or is there an excessive rise in a limited group, who as they get older emerge from the normal population owing to the development of a specific disease, essential hypertension?

(8) How often does "transient" or "intermittent" hypertension lead to established hypertension—i e., is there a definite sequence in the natural history from transient to permanent elevation of the blood-pressure?

(9) Can a prehypertensive state be recognised in which metabolic or vascular responses may make it possible to anticipate the development of essential hypertension?

(10) What part do nervous, renal, and endocrine mechanisms play in determining peripheral vascular resistance? Is there any real evidence that these factors play a different role at different stages of the disease?

(11) Is the regional distribution of increased peripheral resistance the same in all cases? Is it different in the early and late stages, and does it differ from the distribution in other hypertensive disorders such as renal hypertension?

(12) Is it possible that, with advancing age, some alteration in the vessel wall may produce a change in reactivity to physiological stimuli?

For the various topics in the symposium, discussion leaders were appointed, and produced a day-to-day progress report In the final discussion on "topics and future trends for research arising from previous discussions " an attempt was made to coordinate the results of the conference, particularly with a view to international co-operation in various fields In what follows, I have tried to give a brief account of the general conclusions on the various topics seriatim, but it must be recognised that on some issues there is still considerable disagreement on both the validity and the interpretation of the available evidence, or on its relevance to essential hypertension

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* This article is based on a summary review of the symposium presented to the Czechoslovak Cardiological Society, and a lecture on experimental hypertension to the Czechoslovak Nephrological Society, Prague, June, 1960

Definition and Natural History

On the question of *definition* it was generally agreed that at present there is no satisfactory alternative to the term essential hypertension, indicating " a common form of high blood-pressure without apparent cause " Whilst modern diagnostic techniques are revealing increasing numbers of cases due to specific lesions, such as renal-artery stenosis, pyelonephritis, or endocrine disease, this is almost certainly a minority group—not large enough, for example, to invalidate epidemiological studies based on measurements of blood-pressure as the sole criterion In the individual it is impracticable to define a critical dividing-line between normal blood-pressure and essential hypertension but this is equally true of other forms of hypertension—e g , that due to renal disease Whether essential hypertension is a disease entity, qualitatively different from the physiological range of blood-pressure, may well be decided by a critical analysis of existing epidemiological data, together with further planned investigation of selected populations If indeed we are dealing with a specific disease, some biochemical fault should eventually be discovered There is evidence that patients with essential hypertension do show qualitative differences from the normal—for example, rapid electrolyte diuresis following plasma-volume expansion by a water or solute load, reversal of the normal antidiuretic effect of injected angiotensin, and the recent evidence of increased secretion of aldosterone in malignant hypertension—but it has yet to be shown that these differences in behaviour are specific for essential hypertension and that they are primary rather than secondary manifestations

One of the most urgent needs is a clearer definition of the *natural history* of the disorder Physiologists, experimental pathologists, and epidemiologists are tending to interpret their various data in terms of the " early " or " late " stages of the disease, but there is as yet no clear understanding of these stages or indeed of the relationship of transient to established hypertension It may well be that further clarification of the natural history will emerge from characterisation of the various states (if these exist) by biochemical or physiological tests Thus, response to salt-loading or angiotensin, or differences in secretion, utilisation, or end-organ response of adrenal cortical hormones, may be found to differ in different clinical groups, or again there may be a change in hæmodynamic pattern in terms of cardiac output and distribution of regional resistance Possibly nervous and humoral factors play different roles in the early and later stages We know, for example, that a minority of cases, especially in young subjects, have an increased cardiac output Whether this is due to anxiety at the time of the investigation and whether it can still be demonstrated after hypertension has persisted for many years needs to be determined Whilst some of these questions—e g , a better definition of stages of the disease—may be answered by large population studies, most of them will require long-term and more detailed investigation of small numbers of patients by the clinician and experimentalist working together For, apart from problems of differential diagnosis, it will be essential to recognise the intrusion of secondary factors, such as local atherosclerosis, altered renal function, or emotional reactions, which may modify the physiological pattern and bring into play new homœostatic mechanisms

Epidemiology

The starting-point of epidemiological studies is the validity of blood-pressure estimation as an index Examination of the " casual " blood-pressure should be made to see whether further standardisation of technique is possible and what additional criteria can reasonably be included in population studies The epidemiologist is on uncertain ground until the validity of the high casual pressure as an indication of essential hypertension is assured But if this can be established, some of the really fundamental problems of ætiology may be solved by epidemiological methods The most important of these is *heredity* If the genetic factor in essential hypertension is of major importance there is an urgent need to seek for an inborn error of metabolism in the pathogenesis of the disease Even if there is a specific genetic factor, the environmental situation may well determine whether this defect leads to manifest disease Furthermore a distinction (commonly overlooked) must be made between genetic factors and the " cultural inheritance " which is also transmitted in the family The influence of *age* is the second main problem which epidemiological studies should be able to resolve, for if a substantial rise in blood-pressure can be shown to develop in a discrete section of the population as age advances, in contrast to little or no rise in the remainder, there can be little doubt that essential hypertension exists as a separate entity, furthermore the search for a causal mechanism can then be directed to changes in function with advancing age There is a good deal of evidence, at present difficult to evaluate, of blood-pressure differences between population groups, which may be related to ways of life It is in the epidemiological field that international cooperation is likely to be most fruitful, particularly in the investigation of racial factors, the effects of diet, the stresses of industrialisation, and other circumstances where differences in prevalence, already recognised, present " experiments of opportunity "

The Neurogenic Hypothesis

The view that essential hypertension has a neurogenic basis is undoubtedly enjoying a new wave of popularity Investigators in the Soviet Union have for some years maintained that essential hypertension develops as a specific manifestation of neurosis, and this has led to observations on the prevalence of hypertension in different occupation groups, to extensive physiological researches on the nervous regulation of the circulation, and to studies in dogs and monkeys of experimental hypertension produced by stress stimuli using conditioned reflexes and Pavlovian techniques The widespread use of hypotensive drugs which act centrally or peripherally by inhibiting autonomic vasoconstriction has produced in some quarters an uncritical acceptance of the neurogenic theory, or at any rate of an important nervous component in essential hypertension Supporting evidence has been sought, particularly in the United States, by analysing the emotional and hæmodynamic responses of hypertensive individuals to stressful situations, or by studying cultural background, character structure, and behavioural patterns in relation to the incidence of the disease. Owing to lack of translations of published data it is impossible to give a fair assessment of the Russian view, and it is to be hoped that the clinical, experimental, and epidemiological evidence on which this concept is based will soon be made more readily available. At present most workers agree that in the established phase of essential hypertension—i.e., when the diastolic pressure is persistently raised—there is no convincing evidence that the cause is neurogenic vasoconstriction. That emotional stress can cause acute elevation in blood-pressure is undoubtedly true, but the relevance of this to the chronic disorder we term essential hypertension is quite obscure, and in neither transient nor established hypertension has increased autonomic activity been demonstrated by the finding of increased catechol-amine production, as is observed in patients with high blood-pressure due to phæochromocytoma. There is obviously a need for a more critical and broadly based assessment of hypertension of supposedly nervous ætiology in terms of its clinical characteristics, hereditary origins, and subsequent course. Furthermore when studying emotional responses in both personal behaviour and vascular reactivity, it is essential to establish to what extent these are the cause or the result of the elevated blood-pressure.

Hæmodynamic Changes

From what has been said it will be obvious that the largest single obstacle to understanding the genesis of hypertension is an imperfect knowledge of the factors which control the blood-pressure in health. It would be easier to decide whether hypertension was "abnormal" if we understood better the mechanisms by which normal blood-pressure is maintained. This becomes even more obvious when considering the further problems of hæmodynamic changes, vessel-wall factors, and the possible role of renal and endocrine dysfunction in essential hypertension. In the field of blood-pressure regulation, physiologists seem to have been until recently almost exclusively concerned with the autonomic control of vascular tone. In various discussions a great deal was heard about the baroceptors and other vascular receptor mechanisms, about cardiovascular changes following hypothalamic stimulation, and about the central and peripheral effects of hypotensive drugs on autonomic status and catechol-amine production. It is well established that the response threshold of the baroceptors is raised in chronic hypertension, but this appears to be an adaptation to the high blood-pressure rather than its cause. Recent physiological and pharmacological work has certainly revealed new aspects of neurogenic control of the circulation, but those who are concerned with the problem of hypertension, either clinically or experimentally, are questioning the adequacy of this approach, and are seeking information on other possible regulating mechanisms which may be more relevant in maintaining blood-pressure at a high level. For example, what controls the residual arteriolar tone when all sympathetic influences are removed? Is it some endocrine factor, a renal pressor substance such as angiotensin, or is it a question of the electrolyte environment of the smooth-muscle cells of the arteriole? Whatever the controlling factors, vessel tone varies under the influence of a number of stimuli, and this brings up the vexed question of vascular reactivity. Pressor responses to vasomotor stimuli such as cold, emotion, and vasoconstrictor drugs have so far failed to provide a convincing separation of hypertensive from normotensive subjects or to predict the future development of high blood-pressure in the latter. Yet the level of the blood-pressure alone is insufficient to explain individual differences in the production of both functional and structural vascular reactions—e.g., hypertensive headache, papillœdema, fibrinoid arteriolar necrosis and localised cerebral vasoconstriction in hypertensive encephalopathy.

In general the view has long been accepted that narrowing of the arterioles is the primary hæmodynamic change in essential hypertension. An alternative view is that vasoconstriction may occur as a reaction to increased intra-arterial pressure, which might be caused, for example, by a rise in cardiac output. This possibility has directed attention to primary changes in cardiac dynamics and to possible alterations in venous tone or venous blood-volume, which might affect cardiac output and thereby initiate arterial hypertension. Deviations from normal behaviour, such as the rapid salt diuresis in chronic hypertension, and the link between reduction in plasma-volume and blood-pressure after administration of diuretics such as chlorothiazide, have suggested a disturbance in the relationship between vascular capacity and blood-volume in the hypertensive patient. Various new and interesting techniques are being developed in an attempt to explore these possibilities. Methods have been devised for a more exact physical analysis of the parameters of vascular tone, and it is hoped that these may provide a means of identifying and assessing the effects of neurogenic and humoral factors, and of vascular "reactivity", in hypertension of various sorts. Hæmodynamic studies on cardiac output, and on the regional distribution of peripheral resistance, suggest that in hypertension certain areas of the vascular bed—e.g., the kidneys and skeletal muscle—respond differently in different circumstances. Experimental models are also being devised in animals in an attempt to separate the cardiac component from the role of the peripheral circulation during changes in blood-pressure induced by various means.

Metabolic Factors

The symposium included a number of papers and a very critical discussion on the role of pressor amines, the adrenal cortex, and renal factors in the pathogenesis of essential hypertension. Most workers agreed that at present there is no direct or convincing evidence that either the kidney or the endocrine system plays a part in the early or later stages, although this may not be true in the malignant phase of the disease. Here again we are faced with the problem of distinguishing primary factors from secondary changes which develop in severe hypertension as a result of renal vascular damage. Such damage may produce metabolic disturbances—for example, in sodium and water excretion—and may possibly alter the pattern of hormone production (e.g., hyperaldosteronism in malignant hypertension). Nevertheless recent work on the reciprocal action of renin and aldosterone, and on the relationship of renin production by the juxtaglomerular apparatus to renal perfusion pressure, have produced, if not yet a promise, at any rate a hope, of a clearer understanding of renal participation in blood-pressure regulation.

There is another line of approach, based on both clinical

and experimental observations, which is certainly relevant to the problem of chronic hypertension in general, and possibly by analogy to essential hypertension This is the growing evidence of a change in mechanism when high blood-pressure passes from the acute to the chronic stage Thus when hypertension is caused by some specific lesion—e g , phæochromocytoma, adrenal cortical tumour or unilateral renal disease—the pressure frequently remains elevated when the primary cause is removed As far as present evidence goes, it does not seem possible to distinguish this chronic residual hypertension from essential hypertension on clinical, physiological, or anatomical grounds There is some evidence also of a difference in mechanism between the hypertension of acute and chronic nephritis and early and late experimental renal hypertension These observations underline the importance, first, of looking for a similar change in mechanism in the development of essential hypertension, and, second, of considering the possibility of a common factor in the various forms of chronic high blood-pressure The striking thing is that in all these conditions a new equilibrium appears to have been established at a high level of blood-pressure which is consistent with many years of good health This would appear to involve a " resetting " of the homœostatic mechanisms which normally maintain arterial pressure at a steady level There is evidence of such a resetting in the case of the baroceptors, but, as already mentioned, the evidence does not suggest that this is of causal significance One of the most clear-cut observations in this field is the reversibility of chronic renal hypertension In the laboratory animal, renal hypertension of long duration is reversed within a matter of hours if the renal circulation is restored to normal In man a similar prompt reversal of chronic renal hypertension has been demonstrated when, in identical twins, a normal kidney has been grafted in a twin with chronic nephritis and the diseased kidneys removed Thus it is clearly established that, in the maintenance of chronic renal hypertension, no irreversible extrarenal mechanism—structural or neurogenic—supervenes This does not of course exclude the participation of some extrarenal factor, but it does indicate that in this form of chronic hypertension a metabolic renal disturbance almost certainly plays a primary role in resetting the homœostatic regulation of the blood-pressure at a higher level In other forms of chronic hypertension, including essential hypertension, this line of reasoning is effectively blocked by the fact that, at any rate until the late stages, there is no structural basis for a renal mechanism If therefore the kidney plays a role in the pathogenesis of essential hypertension it must be on the basis of a purely functional disorder, or of structural changes which have not been so far revealed by light microscopy This is a main problem for future investigation One of the most urgent needs is a further clarification of the mechanism of renal hypertension, for, from what has been said, this may open the way to an understanding of other forms of chronic high blood-pressure

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Inevitably the status of the practitioner (he could now hardly be called family doctor) had suffered—and this at a time when in the higher administrative places opinion was moving away from increased institutional treatment, particularly of mental illness, of the very young and very old, and even for midwifery

Those who served on executive councils should welcome this rethinking, and should determine forthwith to play a more creative part in building a complete domiciliary service—an aim which could be achieved only in cooperation with the public-health, hospital, and social services The general practitioner could then become more of a personal doctor, concerned with the social aspects of disease, able and willing to advise the family on its problems, the children, the aged dependants, and the difficulties when the family had to cope with a mentally ill member

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Another difficulty, which had been only half faced, was the general practitioner's security, or lack of it The doctor should have the right, without fear of losing his patient, of advising the patient firmly on the course he should pursue, and not merely prescribe the latest tablet A change of doctors should not be allowed without adequate grounds Finally, there should be some recognition of higher standards of work

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The significance of the rheumatoid serum factors was discussed by Dr J Ball (Manchester), who said that the rheumatoid macroglobulin factor for rabbit globulin could be detected in about 40% of adults, and in significant titre in 2–5% of Northern Europeans Positive tests were found (apart from rheumatoid arthritis) in a significant proportion of cases of S L E, systemic sclerosis, digital arteritis, and Sjogren's syndrome About 35% of positive tests in a random sample were associated with clinically detectable disease.

Dr C L Greenbury (Stoke Mandeville) described quantitative experiments using radio-iodine to label rheumatoid factor or antibody, which indicated that the amount of factor removable by repeated absorption from a given serum varied according to the degree of sensitisation of the absorbing red cells

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Dr J. N. McCormick (Stoke Mandeville) had used partially denatured human γ-globulin labelled with fluorescein to detect rheumatoid factor in unfixed frozen biopsy material from rheumatoid arthritis. The cells containing the factor were mainly plasma-cells, and were most numerous in rheumatoid synovial tissue. The globulin of the germinal centres, although abundant, appeared to contain very little rheumatoid factor.

Fluorescence methods of locating tissue antigens (using fluorescein and rhodamine conjugates) were also described by Dr G. Scott (Stoke Mandeville). Using anti-glomerulus and antisynovial-membrane conjugates, he had defined three components of human connective tissue by immunohistochemical staining.

Dr W. R. M. Alexander (Edinburgh) had found that synovial fluid from rheumatoid-arthritis patients injected intradermally in other patients or controls, often gave rise to a delayed skin reaction, apparently of the Mantoux type. The active factor, a γ-globulin, was very unstable, and usually did not cause a reaction in the donor's own skin.

Discussing his experience with antinuclear serum factor as revealed by the fluorescent-antibody method, Dr D. M. Weir (Taplow) said that the factor was almost invariably present in S.L.E., but was also found in rheumatoid arthritis, discoid lupus, and some other related conditions, although much less frequently and usually in lower titre. He described laboratory investigations on the nature of the antigen(s) reacting with the serum factor.

Dr G. J. Friou (Yale) had studied antinuclear factor using fluorescent and radioactive labelled antihuman globulin with whole nuclei, and nucleoprotein, as antigens.

Dr W. Hijmans (Leiden) regarded the L.E. cell factor as an antibody against nuclear material, and described quantitative precipitin studies between desoxyribosenucleic acid and serum, and complement-fixation studies with histone. He gave reasons for not considering the serum factor as pathogenic.

Dr E. J. Holborow (Taplow) considered the antigenic possibilities of the polysaccharides of connective tissue. He outlined natural and experimental methods of enhancing antigenicity of polysaccharides and drew attention to the lack of knowledge of whether they could take part in hypersensitivity reactions.

Medicine and the Law

The New Criminal Justice Bill

This Bill deals mainly with offenders under 21. Its main objects are to make wider provision for the use of borstal training and of detention centres in dealing with young offenders, to discontinue short sentences of imprisonment as more detention centres become available, and to extend the provision of compulsory aftercare. Changes are also proposed in the law relating to approved schools.

Part I remodels the custodial forms of treatment for young offenders. No new forms of treatment are proposed, but existing methods, particularly borstal training and detention centres, are extended to more offenders. Imprisonment will eventually be restricted to cases where no other sentence is appropriate. The new scheme depends on the provision of more borstals and more detention centres, and will be introduced by stages as the additional institutions are ready.

Borstal Training

The minimum age for a sentence of borstal training is lowered from 16 to 15 and the court will be able to pass such a sentence whenever they think it expedient that the offender should be detained for training for not less than six months. But if an offender is under 17, the court, before passing a borstal sentence, must decide that no other method of dealing with him is appropriate. The maximum term of borstal training is reduced from three years to two years and the minimum term from nine months to six months.

Imprisonment

The imprisonment of young offenders is restricted to sentences of not more than six months or long sentences of three years or more (except for some offenders who have already been in prison or a borstal). Short sentences of imprisonment are to be abolished by stages as more detention centres become available. Imprisonment of offenders under 17 is abolished, but the power of the higher courts to sentence children and young persons found guilty of grave crimes to detention as the Secretary of State may direct is extended. At present, this power is confined to offences of attempted murder, manslaughter, or wounding with intent to do grievous bodily harm. The Bill extends it to include any offence for which an adult could receive a sentence of 14 years' imprisonment or more.

Detention Centres

Where the court decides that a short period of training is appropriate, the offender will be committed to a detention centre. For offenders until 17 dealt with by a magistrates' court, the period of detention will be a standard term of three months. The higher courts will have discretion to fix the period of detention within a minimum of three months and a maximum of six.

Approved Schools

The law about committal to an approved school is not altered, but the Bill provides that a boy or girl of not less than 15 can be removed temporarily from an approved school on a justice's warrant, if this is necessary to maintain discipline, to another approved school, a remand centre, or a remand home for up to twenty-eight days. Offenders who turn out to be unsuitable for approved-school training, but are likely to benefit from borstal training may, with the consent of the Secretary of State, be brought before a magistrates' court, which will have power to order their transfer to borstal.

Attendance Centres

The minimum age at which a child may be ordered to attend at an attendance centre is reduced from 12 years to 10.

Fines

New and, in general, higher limits are set to the fines that magistrates' courts may impose in respect of offences committed by children and young persons, and the obligation on a parent to pay damages of costs awarded against his child is extended to the payment of compensation for loss. Enforcement of fines will be by committal to a detention centre or a remand home for offenders under 17.

Compulsory Aftercare

This is usually undertaken by probation officers. It is extended for the first time to all offenders who are released from a detention centre (unless they were sent there for a default) and to some categories of people released from prison. The extension of compulsory aftercare to ex-prisoners will be introduced by stages. When it is completed it will include all sentences of four years or more whatever the age of the offender, all sentences of six months or more where the offender was under 26 at the start of the sentence, and all sentences of six months or more when the person has previously had a prison sentence of three months or more or a borstal sentence.

In England Now

A Running Commentary by Peripatetic Correspondents

ONCE again the Director-General's Exercise—this year named White Swan—gave us a programme packed with interest, a shop-window of ideas for the future. Some will be discarded, but others will bear fruit. I asked three very senior officers what was the biggest problem facing the Army Medical Services today. One said the acquisition of broader professional experience. Another said the recruitment of other ranks (and gave me an entertaining lecturette on how to do it). The third said transport, transport, and transport again. If you can transport the sick and wounded, quickly and shocklessly, over long distances to the medical centres, you can economise in medical manpower and equipment—and that appeals both to the operational commander, who wants to slim his administrative tail, and to the manpower planner, faced with a return to voluntary service after twenty years of conscription. Transport today and tomorrow means air transport (the day after tomorrow it may mean hovercraft or rockets) and the D.G. duly showed us long-range aircraft, the rotodyne, helicopters—the lot. A French general told us about the enormous use made of helicopters by the French army in Algeria. The six-year-old Algerian war has given the French more experience than any other nation of air evacuation, but he indicated that the French Army did not want to go on accumulating this experience.

We also saw the latest types of civil ambulance cars, some with bodies completely constructed of plastic reinforced with glass-fibre, which is strong, light, rustless, and never needs painting. Yet with road congestion getting worse every day, will not the local health authorities have to invest in helicopters? Let the R.A.M.C. show the way. At the Cambridge Hospital they could establish an accident centre, equipped with helicopters and aerial cameras, to serve the whole of the Aldershot district. The casualty department would be staffed with surgeons of the requisite experience, a helicopter-ambulance could be at the scene of an accident in a matter of minutes (even on bank holidays), and every accident could be photographed from the air. What a contribution such a unit could make to research into the causation, prevention, and treatment of road accidents!

An excellent curry—made with dehydrated ingredients and served in a hangar—revived our spirits after the cold of the airfield. We saw the impressive efforts which are being made to modernise and improve military medical equipment. The Plastic Age is dawning, and the reductions in total weight and bulk are nothing short of dramatic. The new lightweight medical panniers were demonstrated by an extremely smart Nigerian private who has won the Duke of Edinburgh's gold award.

I am not yet convinced of the value of the universal container—a lightweight room that can be carried by air and deposited on any little flat piece of ground. We saw it being used as an operating-theatre, as a pathology laboratory, as an advanced medical store, as a heatstroke centre, and as the examination and treatment room for a 10-bed medical reception station. Perhaps it was the sight of ten "patients" lying in bed in the pouring rain (were there not enough canvas roofs to go round?) that made me feel that further experiment in the design of tentage and supports is what is really needed. The School of Health gave us an admirably straightforward demonstration of ten basic health routines for the soldier, after which there was a bit of a barney about urine tests for paludrine.

The Exercise gets more like an international congress every year. None of the American officers would hazard a guess on the result of the Presidential election. Eminent officers from the Indian subcontinent spoke to me gloomily about the changed status of their 2000-year-old Maginot Line of the Himalayas. A Canadian officer told me that the integration of the Canadian Forces medical branches (which so bewitched our political mentors in the Select Committee on Estimates) had scarcely changed anything. Just at present, integration seems to be more urgently needed in certain political circles than anywhere else. At the Exercise supper a well-known authority on malaria prevention presided with patriarchal dignity over a table of pretty nursing officers, and somebody round the piano sang "I'm Dreaming of a White Swansong".

* * *

I am, I confess, a secret thinker, and one day in the rush-hour I caught myself at it again. Suppose a Neptunian scientist (people on Neptune are very large) knowing nothing about life on Earth were to hover over some of our greater cities, studying the traffic. He would notice that the multi-coloured shining particles which moved in certain natural channels appeared to obey certain laws. These laws, it is true, would not always be rigidly followed, they would be approximate, statistical, stochastic laws, similar to those of chemical kinetics and thermodynamics in our own scientific culture. He would observe, for example, that when a space appeared among a stream of particles, one of them would inevitably sooner or later move into the gap, so that the place left behind it could in turn be filled by another particle and so on, giving the overall effect of a sluggish wave-like forward motion. He might well postulate some kind of force, tending to move the particles by mutual pressure into regions of low population density. "Nature", he might aphoristically say to himself, "abhors a vacuum." Or he might notice that when the population-density was high, the noise-level also tended to be high, or there might be a relation between the average rate of the forward wave-motion and the density, or between the noise-level and the mean distance travelled without collision. In short, our Neptunian might soon build up a set of traffic laws akin to the gas laws of physics.

At this point in my meditations I stopped my forward wave-motion with something of a jolt, causing a transient sharp rise in the local noise-level. If a Neptunian were to look on us like that, would he be doing anything fundamentally different from what we do when we study the molecules of a gas? And would it ever occur to him that each one of those curious shiny particles, with their semi-random, semi-determinate motions, might contain a living, sentient, meditative being such as myself? Well, then, how about the gas molecules? Who might there not be inside them, I asked myself. And, do you know, the thought has bothered me since. After all, how do we know that an atom doesn't think of itself as ME? It's time somebody looked into the matter, in my opinion, because if we go on treating the atoms the way we do now, some day there'll be trouble.

* * *

We had a rotten trip back fom the States. Even the official log of the *Mauretania* described the conditions as "strong N'ly gale, very rough sea, very heavy N'ly swell". After long deferment of hope in successive arrivals at Cobh and Le Havre, we reached Southampton. I telephoned my wife and arranged for her to meet me in Newcastle at 7 A.M. The boat train took me to London, where I boarded the sleeper at King's Cross.

I woke up at 6 A.M., and reflected that this was the ninth day since leaving New York, but that I would be home in an hour. The attendant brought tea. I remarked that it seemed very quiet outside. "Yes, Sir," he said, "I'm afraid we're still in Northallerton, and we're an hour behind time. I'm just going to find out what's the matter." He was back in a few minutes to say "It seems, Sir, that the fire went out. They're busy trying to get it going again."

Not even the rich new expletives that I had learnt in America were of any use to me. I was speechless.

* * *

Our quiet, shy, third-year medical student disappeared behind the screens to examine a middle-aged blonde patient. All was well for a few minutes as his examination proceeded, but suddenly the quiet of the ward was shattered by scream upon scream and the words "I wouldn't even let my husband do that." The student emerged blushing furiously to explain to

Sister, who advanced in a menacing way, that he had only been eliciting the patient's plantar responses

* * *

A long time ago I made the mistake of learning how to use a desk calculating machine It was useful to me at the time, because I do not like doing sums and it was much nicer to have a thing like a typewriter to do them for me But it got me a reputation which did me no good at all, and I became known as the department's statistician (unpaid and quite extra to my proper jobs) and general calculator-man I have never been strongminded enough either to repudiate the status or to insist on people learning to do sums for themselves Now, to put the seal on my position, I have been sent on a computer course because " it might be useful if you get the know-how "

I must say the computer people were very nice and friendly to us (I could be friendly too, if someone wanted to learn from me how to use my little desk machine instead of wanting it done for him) Their machine was friendly too, a bit dour the first time we called on him, but then he was said to have a pain in his inside, and an appreciable smell of beer in his neighbourhood suggested that he knew how to look after himself when out of sorts Later he was in splendid form, inverting a large matrix and playing a happy tune on his hooter to announce progress after each thousandth sum or so—i e , a brisk toodleoodleoo, with a thousand to each " ooo " Our job, it appeared, was to learn a language which he could understand well enough to translate into his own dialect, and presently we were writing

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A = 2
B = 2
A = AB
PRINT (A)
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which seemed a funny way of putting 2 × 2 and downright wrong algebra But presently we grasped bits of it, and were happily composing letters to the supermachine and even typing them ourselves on the teleprinter which makes the only kind of signs he is really interested in reading

By the end of the course the real mathematicians had become obvious, while some amateurs had fallen by the wayside altogether This was not quite my fate, but I did get a bit mixed up about what was computer-work and what was not I wandered into the unit's common room and was interested to find *The Times* with the crossword only half done The supermachine couldn't have been too slow to finish, it was nice to think that in some ways he might have been too stupid But then computers are apt to have a streak of stupidity look at me still doing the department's sums for them I never thought that this course would show me that what I have most in common with supermachines is a willing nature

* * *

Aunt Pash must be one of my oldest patients She is said to be 93, has one eye, and a colostomy She lost her eye in " one of they girlish pranks " I am not sure what she means by that, but knowing Aunt Pash, I fear the worst I usually visit her hut on the beach when I am in that part of the district, but three times lately it has been empty, and neighbours told me that Pash was visiting However, the last time I was up the Bay, she was home again, and her hut was, as ever, chaotic with spinning and quilting This time there were no tales of her girlhood—the more lurid of which always ended with 'Ah, my dear, the tales I could tell'ee, the tales I could tell ee " No, she had been out gallivanting, and mightily she had enjoyed herself A distant cousin had moved house, and she had gone to help Now it may not be remarkable for an elderly lady to hold very small pieces of china at a housemoving, but in Newfoundland housemoving literally means house-moving The house is taken from its foundation, hauled down to the edge of the water, floated on to a raft, and towed to its new site Once there it is dragged out and hauled into position It is a backbreaking job, and all hands are needed on the lines This is what Aunt Pash had been doing on her holiday Later I was told that she had worked as hard as anyone and cussed better than most I don t doubt it at all

Letters to the Editor

FUTURE ORGANISATION OF PATHOLOGISTS

SIR,—Since with the approach of voting-day for pathologists, past-presidents of the Association of Clinical Pathologists have written to press the advantages of the recent " offer " of the Royal College of Physicians, I write to point to one important fact and event in the history of the Association that has been omitted from recent discussion and documents

The Association of Clinical Pathologists became incorporated on Feb 12, 1956 This was the culmination of the labours of a devoted secretary and had been pursued with enthusiasm by presidents, officers, and council, and the members and all knew that this was the initial stage in the formation of a new and independent college

What is it, therefore, that has caused presidents, officers, and council now so eagerly to favour " the present generous and unequivocal terms " of the recent offer of the Royal College of Physicians ?

That a diploma of membership of a division or faculty of a Royal college would be an almost immediate result of acceptance of the offer is certain, and this would meet one of the needs of pathologists without any great effort—merely the subscription of foundation membership, or examination and membership fees But the status that this diploma might confer would be somewhat reduced by the inferiority attaching to a division or faculty (That a faculty is regarded as inferior is witnessed by the current action of a most ancient medical faculty that seeks by legislation to alter its title to Royal College of Physicians and Surgeons of Glasgow) Surely, the seniors in the Association are not unaware of this implication of inferiority which is not disguised by the use of the term division Why is it therefore that they advise a " short-cut " when the Association has progressed to incorporation unaided ? Everyone knows that a new and independent college may require a few years to have its diploma of membership recognised, everyone knows that a new college is not founded and nurtured without great effort and equally great sacrifice Those who earnestly and sincerely consider that an independent college should be the heritage of our registrars, and in turn their registrars, would work willingly and make sacrifices Is it that in the remaining years of their working lifetime the seniors would rather they held high office and examinership in a subsidiary faculty (of which they are fellows through being fellows of the parent college) than be concerned with great efforts the fruits of which would be enjoyed by posterity and not by themselves ? Or, to put it at a higher level, is it that the senior pathologists who are fellows of the Royal College of Physicians are using their influence to secure to this college, at the time of rebuilding, and for a long time, revenue from the pathologists that in the first instance might amount to around £25,000 ?

London, N 18 J F HEGGIE

SIR,—Dr Joan Taylor and Professor Pulvertaft are two of my oldest friends, but I am bound to tell them that most of their letter of Nov 5 is rubbish

Professor Pulvertaft has had much experience in the appointment of pathologists Has he ever found the absence of a specific higher qualification a handicap ? And if so, how often ? (In this debate a few quantitative statements will be refreshing) He makes appointments, as everyone else does, on the confidential advice of his colleagues and on his own judgment If he has made an occasional mistake I have little doubt that it has been when the flutterings of his warm heart have silenced the warnings of his cool head In our lifetime it has been characteristic of pathology—more, I think, than of any other branch of medicine—that it has drawn its adepts from a wide variety of sources the preclinical sciences, public health, and general practice have all contributed colleagues whom we respect There have been those pathologists who combined the humblest medical qualifications with fellowship of the Royal Society It is one of the weaknesses of the N H S that it is more difficult than it was to change from one specialised branch to another To add any degree or diploma which makes the entry into pathology more difficult or more rigid can only impoverish the science

"Academic centre" is, I suppose, looking-glass language for a college or faculty The adjective is an unusual one to apply to any existing body of this kind except, perhaps, the Royal College of Surgeons As for "a body to speak for pathologists", things have come to a pretty pass if Dr Taylor and Professor Pulvertaft are no longer able to speak for themselves To whom is this body to speak and about what? And who on earth would be able to speak for such a disorderly mob of individualists as we are?

In all this interminable debate the talk has always been of examinations and diplomas but seldom of training Is it not time that we abandoned this babu attitude? The Doctor and the Professor and I all learned pathology in the bad old way, picking up knowledge and experience as we could, piecemeal and without a plan The example of the course for the diploma in bacteriology has shown that a more systematic training is not only possible but desirable I see no reason why the same methods should not be applied to other branches of pathology if some university will give them a trial

Hoccombe, Somerset J A Boycott

Sir,—For Dr Joan Taylor and Professor Pulvertaft I have the greatest admiration and respect, but their idea of an academic centre for pathology in London seems completely out of touch with the ideas of those of us who work some distance from London

The higher qualification and the body to speak for pathologists can be achieved at a very small cost Dr O'Gorman (Nov 5) is rightly daunted by the cost of a building, but what pathologist outside London is going to use such a building?

For meetings, the Pathological Society and the Association of Clinical Pathologists have been able to enjoy the hospitality of numerous bodies all over the country The College of Pathologists could do likewise

Why should not the College of Pathologists start in a small way like the Royal College of Obstetricians and Gynæcologists?

As for withdrawing, as Dr O'Gorman suggests once we are in the Royal College of Physicians it will be impossible to withdraw from that body without its permission The constitution of that body is authoritarian, and it would be unreasonable to expect permission to withdraw to be granted, as G G implies (Nov 5, p 1025)

No, Sir! The only solution appears to be the logical conclusion of Peter Davey's argument He says that the physicians are notable Greek scholars They therefore know that a pathologist is a man who studies disease Their work is therefore pathology, not physic, which is the study of Nature

Let them show their greatness by changing their name to the Royal College of Pathologists We will then join in with them, so possibly will the other Royal Colleges! (Or am I optimistic?) We shall then have a body able to speak for the whole of Medicine

The alternative more likely to be acceptable is for the pathologists to have their own College, and for all the medical colleges, faculties, associations, and societies to join together to form an Academy of Medicine for that purpose

Mumbles, Swansea H C M Walton

Sir,—As an ordinary pathologist of a very peripheral hospital, may I support the plea of Dr Joan Taylor and Professor Pulvertaft for a vote in favour of the division of pathology within the Royal College of Physicians I started this year firmly in favour of an independent college and, because of the accident that it was my turn to be branch president, found myself defending this view on behalf of the North of England branch at a special meeting of the council of the Association of Clinical Pathologists held in February Because of this I subsequently had quite a long exchange of views with various members of the council, and have since become convinced that a division within the Royal College of Physicians will meet our needs

In the Widdicombe File, G G discusses the various obstacles in the way of an independent college and shows how they might be overcome, but he does not mention the greatest obstacle of all This is that the great majority of the leaders of our specialty do not favour the establishment of an independent college at the present time, but, in all sincerity, prefer the R C P solution It seems to me that it is possible and right for the main body politic of the Association of Clinical Pathologists to stop—if it so wishes—its leaders from going a certain way, but more than this is not possible The real issue in the forthcoming poll therefore is not between the R C P and an independent college but between the R C P and nothing at all for many years to come With the Royal Commission finished, the next ten years may be all-important in shaping the future pattern of British medicine, and it will be bad for both medicine and ourselves if during this time we alone among the major specialties have no official organisation

Northallerton P N Coleman

Sir,—Discussions on the future of clinical pathology have assumed that it has a future in the form we know today The supporters of a College of Clinical Pathologists ought to discuss this assumption and have not done so, association with the Royal College of Physicians involves considerably less mortgage of the future

We are not endowed with the gift of prophecy Twenty-five years ago few would have envisaged the position that clinical pathology enjoys today To assume that the present pattern will exist unchanged in 1985 is to make an improbable assumption Two branches (hæmatology and chemical pathology) are growing rapidly and show signs of passing out of the ken both of the general physician and of the clinical pathologist Hæmatology is already well on the way to becoming a subspecialty of internal medicine More slowly, chemical pathology is going the same way, the advent of automation, lessening as it must preoccupation with technique, will accentuate this trend Of the other branches of clinical pathology, hospital bacteriology is being divided more and more between the specialists in hygiene and therapeutics Remains pathology proper, the practitioners of which have always had a well-defined subject which does not take them to the bedside nor make them primarily technicians, it is probably the branch of pathology destined to change the least It seems at least unlikely that most of the subject-matters of clinical pathology will remain in the hands of a group called clinical pathologists and a College of Clinical Pathologists, if established, could become another South Sea House and an obstacle to progress

For reasons set out by Dr Joan Taylor and Professor Pulvertaft present action is needed such action should leave the future uncommitted as far as possible Association with the Royal College of Physicians is the only logical course

Sheffield ARTHUR JORDAN

⁂ A letter from the Widdicombe File appears on p 1094 —ED L

USE OF BRL 1241

SIR,—Dr Novick's letter (Oct 29) covers well-trodden ground and adds little except speculation to what we already know By now several thousand strains of *Staphylococcus pyogenes* have been tested, and so far no "celbeninase"-producing organisms have been found This suggests that they are rare if they exist at all, and are considerably rarer than penicillinase-producers were at the time of the introduction of penicillin On the other hand we are all agreed that bacteria often yield mutants which bypass the injurious effects of a chemical agent in some way other than destroying the drug This is an alternative and more common method of developing resistance to an antibiotic In the case of penicillin such mutants can readily be obtained by selection in the laboratory, but have not been shown to be the cause of lesions in man Thus of the two kinds of resistance to penicillin only the one based on the destruction of the drug by an enzyme is clinically important Since 'Celbenin' is a derivative of penicillin having in all probability essentially the same mode of action it would be reasonable to expect that resistant mutants (non-"celbeninase") might also lack pathogenicity, even though retaining coagulase and other characters However, whether this expectation is unfounded, and strains *do* exist which retain sufficient virulence to be of clinical importance and in addition are endowed with sufficient communicability to occupy the biological space in hospitals, can be determined only by carefully controlled clinical observations

The demonstration of celbenin-resistant staphylococcal mutants was probable on general grounds and would be expected to follow the pattern of multiple steps of mutation seen with penicillin, each step resulting in greater resistance As the serum levels obtainable with celbenin at present are more restricted than with penicillin, it is conceivable that first or second step mutants could acquire sufficient resistance in vivo to escape therapeutic action, and yet retain pathogenicity With spraying, however, this is less likely to occur since much higher concentrations can be achieved locally and the mutants succumb to the higher doses of the drug Resistant mutants are not man-made, only selected, and on speculative ground at any rate are more likely to result from therapeutic use than from spraying

Dr Novick says that " it is conceivable that the method might be used indefinitely without unfortunate consequences, and it could be argued that the risk involved is acceptable in view of the advantages This risk must, however, be assessed in the light of the history of the fight against the staphylococcus " We submit that this is precisely what we did—bearing in mind the fundamental clinical problem of penicillin resistance

It must be admitted that a complete victory along these lines is perhaps not in sight, but that should not make one jettison a line of research on theoretical grounds The spraying of carbolic by Lister did not altogether banish hospital gangrene, but while it was in use undoubtedly saved a great number of lives We believe that the discovery of celbenin by the Beecham group was a milestone in the history of antimicrobial agents and will certainly lead to new and powerful drugs in the future In the meantime experiments with spraying should continue until their value is proved or their risk demonstrated on a factual basis

Bacteriology Department,
St George s Hospital
Medical School,
London, S W 1

S D ELEK
P C FLEMING

PROGNOSIS AND ANTICOAGULANT PROPHYLAXIS AFTER CORONARY OCCLUSION

SIR,—In their very valuable article of Nov 5 Professor McMichael and Dr Parry suggest that the unusually good 5-year survival-rate of doctors after cardiac infarction is because "no doubt they can take greater care of themselves and avoid undue physical strain" It is surprising that the authors, who are so rightly critical of loose thinking and imprecision in others, should make such a dubious statement What does "taking care of themselves" mean? And what evidence is there that "avoiding undue physical strain" prevents further infarcts?

I submit that a more plausible explanation of the apparent good prognosis in doctors is that their *minor* cardiac infarcts are more often diagnosed than are the minor infarcts of the laity, the symptoms of which are apt to be attributed to "*indigestion*"

Farnham, Surrey JOHN W TODD

POSTPARTUM PRE-ECLAMPSIA

SIR,—I have read Flight-Lieutenant McFadyen's article of Nov 5 and should like to make the following comments

I have already shown [1–4] that the contracting postpartum uterus provokes renal ischæmia (which incidentally ergometrine might heighten, and this is evident in all the cases reported), that renal ischæmia is responsible for hypertension, œdema, and albuminuria, that hydramnios is an agent provocateur of renal ischæmia (main case), that pre-eclampsia is to be suspected with even minimal signs of the syndrome (main case), that there are many conditions that post partum can masquerade as pre-eclampsia (case 2 certainly being one in point) In fact his case-histories, if interpreted in the light of the data I have provided, amply support the thesis that the uterus resisting tension, which it does post partum also, provokes the uterorenal reflex from which the signs of toxæmia can all stem

Further I have collected sufficient evidence [5 6] to show that the symptomatology of toxæmia is not comparable to Cushing's syndrome, that as toxæmia mounts so do the corticoids decline, that corticotrophin (A C T H) when given experimentally in human pregnancy does not provoke the syndrome, that eclampsia does occur when the adrenals have been previously extirpated, and that the placental production of corticoids is very small in contrast to that of the adrenals

May I also draw attention to two very important data?

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1 Sophian J Toxæmia of Pregnancy London 1953
2 Sophian, J *Excerpta Med* 1958 sec x, 2 no 1
3 Sophian J *Lancet* 1960 i 1351
4 Sophian J *Amer J Obstet Gynec* 1959 78 688
5 Sophian J *Lancet* 1958, i 434
6 Sophian J *Amer J Obstet Gynec* 1954 68, 733

Garrod[7] found that there was an immediate increase in glomerular filtration-rate (G F R) provoked by cortisone experimentally, while there is incontrovertible evidence to show that G F R is much decreased in toxæmia[1]

It would profit obstetricians to study the renal problem deeply To this end may I congratulate you on your enterprise in publishing an account (Sept 17) of the 1st International Congress of Nephrology at Evian, excellently compiled by Professor de Wardener

Worthing, Sussex
JOHN SOPHIAN

CHEMOTHERAPY IN CHRONIC BRONCHITIS

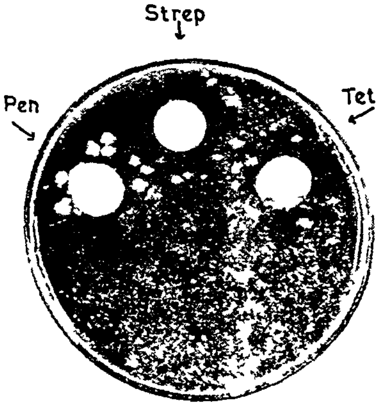
SIR,—The paper by Dr Pridie and his colleagues (Oct 1) and the letter by Dr Aspin and Dr Howells (Oct 15) regarding long-term treatment of chronic bronchitis with antibiotics contain findings somewhat at variance with our own The minimum recommended dose of tetracycline or oxytetracycline for the continuous treatment of chronic bronchitis is 0 5 g daily, but we found 1 g per day to be the minimum satisfactory dose A smaller dose is in our view unlikely to be effective in the treatment of the majority of established cases of chronic bronchitis It does not seem to be a fair test of the efficacy of therapy to use a smaller and relatively ineffective dose With a dose of 1 g daily we have shown that the side-effects are much less significant to the patients than the incapacity which results from acute exacerbations of the disease in untreated cases

Further, the fullest bacteriological information can be obtained only by examining serial specimens of sputum freshly obtained from the patient We have shown that the correlation of the findings obtained from a single isolated specimen of sputum with the clinical state of the patients is poor The mere isolation of organisms not normally found in the respiratory tract, notably the coliform group, had little or no association with the clinical state of the patients, none of whom was treated in hospital

Departments of Infectious Diseases
and Bacteriology
City Hospital, Edinburgh
J McC MURDOCH
J C GOULD

SIR,—I note the letter by Dr Aspin and Dr Howells with particular interest because I have recently been associated with a clinical trial in chronic bronchitis to assess the value of vaccine therapy in contrast to the normal procedures of chemotherapy and antibiotic treatment

During this trial samples of sputum from some 50 patients were examined and we were particularly struck by the suppression of the normal flora with stimulation of growth of coliforms in vitro, using antibiotic-disc technique (see fig)



Stimulation of growth of *Klebsiella pneumoniæ* by antibiotics in sputum-culture from case of chronic bronchitis

This has led us to believe, as your correspondents suggest, that in treating chronic bronchitis intermittently with antibiotics the suppression of the usual flora may lead to consequent increased growth of the coliform organism

We have therefore persisted in our researches to determine what help vaccine therapy could give

We have been using a polyvalent oral vaccine for this purpose, and have had a great deal of assistance from general-practitioner colleagues in this project Should any of your readers be interested in helping us undertake a larger scale trial we should be grateful to hear from them and supply them with the necessary vaccine

Woodlands,
Windlesham, Surrey
R E DEREK LEIGH

SURGICAL REMOVAL OF BRANCHIAL SINUS

SIR,—I should like to congratulate Mr Allan Small on his article of Oct 22 Whether the condition is fistula or sinus is still a debatable point, but at The Hospital for Sick Children, Great Ormond Street, there have been many true fistulæ

This has been proved by the injection of dye into the track and its detection in the pharynx even before operation

The only point in the article that causes some concern is that related to thyroglossal cysts and their tracks I presume that Mr Small implies that the more difficult part of the dissection includes the excision of part of the hyoid bone and the very careful removal of the proximal part of the track as far as the foramen cæcum

If this point is not strongly stressed I am sure that the recurrence-rate in this condition will increase and lead to many more difficult secondary operations

The Hospital for Sick Children,
London, W C 1
S J COHEN

SIGNIFICANCE AND CLASSIFICATION OF FAT-EMBOLISM

SIR,—In his important paper of Oct 15 Dr Sevitt concludes that pulmonary fat-embolism produces no significant ill-effects in previously healthy subjects, and that it does not cause death even in those suffering from shock or blood-loss The validity or otherwise of this conclusion is of great practical importance, for it must influence the rationale of treatment If pulmonary fat-embolism is harmless then the thing to be avoided at all cost is systemic spread of the emboli, for there is general agreement that systemic fat-embolism is potentially a very serious condition Acting on this belief, some German workers[1–3] have practised a prophylactic regime whose object is the maintenance of " controlled hypotension ", in order to reduce the risk of pulmonary fat-emboli being forced through into the systemic circulation

I am less certain than Dr Sevitt that pulmonary fat-embolism is innocuous when very severe or when associated with shock or hæmorrhage The absence of a *characteristic* clinical symptom-complex does not necessarily mean that the condition is free from clinical manifestations of any sort It must be conceded that intravenous injection of fat in animals may produce severe effects and even death, although the lethal dose may be considered high there is a considerable species difference in tolerance—the dog, for example, is much more tolerant than the rabbit[4 5]—and results should not be applied uncritically to man Furthermore, there is abundant evidence that processes such as bleeding or the induction of tourniquet shock much reduce the tolerance of animals to intravenously injected fat[4–8] The contrary finding of Armin and Grant[9] stands alone and

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7 Garrod O , Davies, S H , Cahill, G J *J clin Invest* 1955, 34, 761

1 Fular, W , Kraft, E *Arch klin Chir* 1954 278, 548
2 Fular W Kraft, E *Medizinische* 1956 35 1197
3 Kronke, E *Arch klin Chir* 1956, 283 466
4 Harman J W Ragaz P J *Amer J Path* 1950 26 551
5 Halasz N A , Marasco J P *Surgery* 1957, 41, 921
6 Gold, E Loffler, E *Z ges exp Med* 1923 38, 153
7 Moser H Wurnig, P *Arch klin Chir* 1954, 278, 72
8 Whiteley, H W *J Path Bact* 1954 67, 521
9 Armin J , Grant, R T *Clin Sci* 1951, 10 441

may be attributable to the very small dosage which they employed

Degrees of pulmonary fat-embolism much more severe than that defined by Armin and Grant as " gross " are not uncommon in man [10] Certainly these are the cases in which fat-emboli are most likely to spread systemically, but it is also in such cases that changes due to pulmonary embolisation are liable to be erroneously ascribed to the effects of systemic involvement Although the pathological changes in the lungs—œdema, congestion, and hæmorrhage—are not in any way specific this does not exclude a causal relationship, and in any event the effects of pulmonary fat-embolism may be circulatory as well as respiratory [11] In my experience a predominantly intra-arteriolar and intra-arterial distribution of fat emboli in the lungs is often associated with a short survival time and an absence of systemic embolisation [10] Any system of grading the severity of embolisation should take cognisance of the size and situation of the emboli as well as of their numbers

While the arrest of fat emboli in the pulmonary vasculature undoubtedly protects the systemic circulation it can hardly be regarded as other than a pathological event, I submit that pulmonary fat-embolism should not be entirely discounted as a cause of illness and even death

University Department of Pathology
Western Infirmary,
Glasgow

A J WATSON

TRIGEMINAL NEURALGIA

SIR,—Professor Dechaume has very kindly sent me two papers [12] [13] in which he cites the temporomandibular joint as a potential source of true trigeminal neuralgia I was unaware of these papers when I wrote my letter of Oct 1, and I apologise for that omission Professor Dechaume suggests a method of treatment which is new to me—namely, that the sympathetic enervation of the joint is an effective means of breaking into the vicious circle of effect aggravating cause

Colchester

MICHAEL FROST

NICOTINIC ACID IN ISCHÆMIC DISEASE

SIR,—Dr Archibald's criticism (Oct 8) of bus-drivers resuming their occupations after a coronary thrombosis is very pertinent, and it was only after very careful consideration that these drivers were allowed to go back to work Dr Archibald in effect poses the question " Should all patients who have had a coronary thrombosis be forbidden for that reason to drive a car ?" With the usual treatment, I should be inclined to say " yes ", but I would stress that there is a basic difference with the treatment described in my article of Sept 24

It is interesting that Hunter [14] has described results after nicotinic-acid therapy comparable with my own, except that his dosage is smaller, and he concludes that the improvement in angina is maintained so long as treatment is continued, and that angina gradually returns when treatment is stopped This is in accord with my experience over the fifteen years I have used this treatment, both after infarction and in angina, and it is for this reason that I came to the considered conclusion that ischæmic disease is probably a deficiency disease mainly of nicotinic acid, possibly also of pyridoxine (which forms a coenzyme mediating transaminase reactions and which is probably involved in the enzyme, glutamic-oxaloacetic transaminase) According to this concept, nicotinic acid is a physiological corrective of ischæmic disease

The first patient cited, who is an insurance agent, tells me he makes more than 100 calls a day in his car, and he has done this now for a long time The bus-drivers are seen and examined twice a quarter

Rothwell Haigh,
near Leeds

C E GOLDSBOROUGH

THE VERY DEAF CHILD

SIR,—The complaint of this school, which admits many children who have received various forms of home training, an important aspect of the work of most audiology clinics, is that the period before entry to school for most of them has been inadequately used

Of the present roll of 40 children, 32 have had preschool help of this kind, varying in length from six months to four years 30 of these children had hearing-aids issued by the clinics 2 were deemed too deaf to profit from an aid, though the parents of 1 bought a commercial model

Of the 31 with hearing-aids, only 4, however, were wearing them correctly—i e , continuously and at the right setting with an ear-mould which fitted sufficiently well to enable the necessary volume to be reached without acoustic feedback

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Nursery School for Deaf Children,
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B I INGALL

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Radcliffe Infirmary,
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W I CRANSTON

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We have worked a 3-team system here for ten years, and I support wholeheartedly the doctrine of full clinical freedom for all consultants, indeed, my consultant colleagues here have never complained to me of any interference with their work, but much tact and tolerance are needed on both sides if the hospital is to function smoothly as a corporate entity Dr Kidd tells us that he is responsible to his management committee for the efficiency of the medical work of the hospital How does he equate this personal responsibility with the " full responsibility " of his colleagues ?

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The Mental Health Act has defined responsible medical officers as those in charge of the treatment of the patient Responsible to whom, and for what ? Does " treatment " include control of liberty, food, clothing, social and occupational activities, pocket money, and all the many other aspects of a patient's life ? If so, the result could be chaos with as many " systems " as there are consultants

The duties, responsibilities, and powers of medical superintendents have never been clearly defined No official guidance has been given, presumably in pursuance of the well-known technique of leaving decisions to the man on the spot, with the useful loophole of blaming him afterwards if trouble arises

Responsibility implies authority to take any necessary action, but the authority of the superintendent is vague in the extreme Now that consultants, rightly so, are undertaking greater responsibilities, the functions of the medical superintendent are more than ever in need of clarification This should be done as a matter of urgency, before there occurs some such trouble as that depicted above, with the inevitable recriminations which would follow

Superintendents have " carried the can " for a long time, but, in a changing world, it would be helpful to know something of its new contents

Bracebridge Heath Hospital,
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W A S FALLA

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I am afraid, however, that Dr Kidd's exposition of the medical superintendent's position in regard to administration involves apparent contradictions and several false or dubious premises, as exemplified by the suggestion that " as far as the hospital management committee is concerned he is answerable to them for the efficiency of the medical work of the hospital " I can only think that in this context " answerable " means " responsible " in which case the proposition is quite untenable A medical superintendent working on a basis of clinical equality with his fellow consultants and without powers of clinical interference cannot be " answerable " for the efficiency of the medical work of the hospital It is very relevant that the Mental Health Act, 1959, Memorandum on parts I, IV to VII and IX, paragraph 29, describes the " responsible medical officer " as " not responsible or answerable for the patient's treatment to any other doctor "

Dr Kidd, having listed various coordinating and facilitating functions of the medical superintendent, all of which, I suggest, can be done as well by the chairman of the medical advisory committee, goes on to say that such work can " perhaps be better done by a man who is permanently appointed to the office, because he has powers of decision and authority not available to an elected chairman of a medical staff committee " These powers and authority appear to derive from his being " officially recognised as responsible for medical organisation " This official recognition has the interesting—and highly undesirable—result that hospital management committees "have to take more notice of his monthly reports than the resolutions of medical advisory committees '

This is precisely the situation which consultants in many mental hospitals are no longer prepared to tolerate, especially in view of the fact that as from Nov 1 such hospitals will operate on the same basis as general hospitals All boards of governors of teaching hospitals and the management committees of most general hospitals recognise and " take notice " of their medical advisory committees as represented by an elected chairman Dr Kidd has made no case why management committees of mental hospitals should not do the same Such recognition should be based on the principle that the senior medical staff in any hospital have an equal and shared responsibility for reaching an agreed policy on all administrative matters affecting the hospital as a whole and that the essential administrative work of the medical superintendent or chairman of the medical advisory committee is to facilitate the carrying out of such agreed policy This may involve difficult negotiations with hospital management committee, regional hospital board, hospital officers, and others In such situations the

may be attributable to the very small dosage which they employed

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[2] *ibid* p 19 (reference to the definition issued by the Conference of Executives of American Schools for the Deaf, 1937)

Degrees of pulmonary fat-embolism much more severe than that defined by Armin and Grant as " gross " are not uncommon in man[10] Certainly these are the cases in which fat-emboli are most likely to spread systemically, but it is also in such cases that changes due to pulmonary embolisation are liable to be erroneously ascribed to the effects of systemic involvement Although the pathological changes in the lungs—œdema, congestion, and hæmorrhage—are not in any way specific this does not exclude a causal relationship, and in any event the effects of pulmonary fat-embolism may be circulatory as well as respiratory[11] In my experience a predominantly intra-arteriolar and intra-arterial distribution of fat emboli in the lungs is often associated with a short survival time and an absence of systemic embolisation[10] Any system of grading the severity of embolisation should take cognisance of the size and situation of the emboli as well as of their numbers

While the arrest of fat emboli in the pulmonary vasculature undoubtedly protects the systemic circulation it can hardly be regarded as other than a pathological event, I submit that pulmonary fat-embolism should not be entirely discounted as a cause of illness and even death

University Department of Pathology
Western Infirmary,
Glasgow
A J WATSON

TRIGEMINAL NEURALGIA

SIR,—Professor Dechaume has very kindly sent me two papers[12 13] in which he cites the temporomandibular *joint as a potential source of true trigeminal neuralgia* I was unaware of these papers when I wrote my letter of Oct 1, and I apologise for that omission Professor Dechaume suggests a method of treatment which is new to me—namely, that the sympathetic enervation of the joint is an effective means of breaking into the vicious circle of effect aggravating cause

Colchester
MICHAEL FROST

NICOTINIC ACID IN ISCHÆMIC DISEASE

SIR,—Dr Archibald's criticism (Oct 8) of bus-drivers resuming their occupations after a coronary thrombosis is very pertinent, and it was only after very careful consideration that these drivers were allowed to go back to work Dr Archibald in effect poses the question " Should all patients who have had a coronary thrombosis be forbidden for that reason to drive a car ?" With the usual treatment, *I should be inclined to say " yes ", but I would* stress that there is a basic difference with the treatment described in my article of Sept 24

It is interesting that Hunter[14] has described results after nicotinic-acid therapy comparable with my own, except that his dosage is smaller, and he concludes that the improvement in angina is maintained so long as treatment is continued, and that angina gradually returns when treatment is stopped This is in accord with my experience over the fifteen years I have used this treatment, both after infarction and in angina, and it is for this reason that I came to the considered conclusion *that ischæmic disease is probably a deficiency disease mainly of* nicotinic acid, possibly also of pyridoxine (which forms a coenzyme mediating transaminase reactions and which is probably involved in the enzyme, glutamic-oxaloacetic transaminase) According to this concept, *nicotinic acid is a physiological corrective of ischæmic disease*

The first patient cited, who is an insurance agent, tells me he makes more than 100 calls a day in his car, and he has done this now for a long time The bus-drivers are seen and examined twice a quarter

Rothwell Haigh,
near Leeds
C E GOLDSBOROUGH

THE VERY DEAF CHILD

SIR,—The complaint of this school, which admits many children who have received various forms of home training, an important aspect of the work of most audiology clinics, is that the period before entry to school for most of them has been inadequately used

Of the present roll of 40 children, 32 have had preschool help of this kind, varying in length from six months to four years 30 of these children had hearing-aids issued by the clinics 2 were deemed too deaf to profit from an aid, though the parents of 1 bought a commercial model

Of the 31 with hearing-aids, only 4, however, were wearing them correctly—i e , continuously and at the right setting with an ear-mould which fitted sufficiently well to enable the necessary volume to be reached without acoustic feedback

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elected chairman of the medical advisory committee, speaking for the medical staff, *should* carry more weight than a permanently appointed medical superintendent none of whose authority derives from his colleagues

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It will be a pity if the tremendous opportunities for advance offered to mental hospitals by the Mental Health Act are lost by a refusal to accept the above basic principles of hospital administration

Shenley Hospital,
near St Albans, Herts

D BARDON

OBSTETRIC FLYING-SQUADS

SIR,—Dr Vartan's letter of Oct 22 appears to be misdirected, inappropriate and unreasonable Has no-one ever told him that normal childbirth is a physiological process? To compare it with an operation for varicose veins betrays a distortion of outlook which is all too common

Hove

F V GRIFFITHS

RADIOCHEMICAL SYNTHESIS OF TRIIODOTHYRONINE

SIR,—Dr Deutsch (Sept 10) draws attention to the possible formation of ^{131}I-labelled triiodothyronine by the decay of a molecule of thyroxine containing two ^{131}I atoms, and, with this in mind, discusses the results of Gross and Pitt-Rivers [1-3] and of Braasch et al [4] His conclusions assume that in these experiments a substantial number of doubly labelled thyroxine molecules is present Certainly, as regards the work of Gross and Pitt-Rivers, this assumption is incorrect

The relative numbers of doubly and singly labelled molecules depend on the relative numbers of radioactive (^{131}I) and stable (^{127}I) atoms of iodine present The position can be more easily illustrated by referring to ^{131}I thyroxine synthesised in vitro by an exchange reaction In this material labelling can take place in only two atoms, those in the 3′,5′ positions, and not in all four atoms as in the material synthesised in vivo from ^{131}I iodide Mr Holloway and Mrs Pitt-Rivers (Oct 22) refer to the work of Tata [5] on decomposition products of ^{131}I-labelled thyroxine supplied by Abbott Laboratories Assuming that this materal is prepared by the method of Gleason,[6] and that it is not diluted with inactive thyroxine after preparation, we calculate, from the quoted maximum specific activity of 50 mC per mg thyroxine, that 1 mC of ^{131}I is associated with 6 5 µg of iodine in the 3′,5′ positions The weight of 1 mC of isotopically pure ^{131}I is 8×10^{-3} µg, and therefore in the 3′,5′ positions of this product 1 atom of ^{131}I is present to approximately 1000 atoms of ^{127}I This means that for every 2000 singly labelled molecules only 1 is doubly labelled No detectable amount of ^{131}I-labelled triiodothyronine is therefore likely to arise by the process postulated by Deutsch, and the fact that no ^{131}I-labelled triiodothyronine was detected in Tata's work gives us no information on the correctness or otherwise of Deutsch's postulate

The position regarding in-vivo syntheses is more complex Inactive iodine may be present in the so-called "carrier-free" ^{131}I iodide, and dilution with further inactive material may take place during transport in the body to the thyroid gland, and in the thyroid gland itself Before 1954, ^{131}I produced in Great Britain had a specific activity of about 1 mC per µg iodine this implies that about 1 in every 100 atoms of iodine present was radioactive It was this material that was used in the work of Gross and Pitt-Rivers Even had no further dilution taken place in the subjects the number of multiple (i e, double, triple, or quadruple) labelled molecules would be too small to yield a significant amount of ^{131}I-labelled triiodothyronines by decay (assuming that ^{131}I atoms are randomly distributed in the 4 positions of thyroxine, multiple-labelled molecules would form about 1 5% of the total labelled molecules)

The specific activity of ^{131}I produced in Great Britain has increased markedly since 1954 The Radiochemical Centre product is specified as being not less than 10 mC per µg iodine, and individual batches have given 20 mC per µg iodine this latter figure corresponds to 1 atom of ^{131}I in 6 atoms of iodine The proportion of ^{131}I atoms in fission product ^{131}I supplied by Oak Ridge is probably even higher Rupp et al [7] suggest 1 atom of ^{131}I to 1 atom of ^{129}I plus ^{127}I (^{129}I is sufficiently long lived to be considered stable) With material of such high specific activity any dilution with stable iodine in the body before thyroxine synthesis becomes specially important The factors determining the extent of such dilution are too complex for discussion other than by an expert in the field In general it seems reasonable to suppose that the extent of dilution will be relatively large In certain cases this may not be so, and ^{131}I-labelled triiodothyronine might arise in the manner postulated by Deutsch

Radiochemical Centre,
Amersham

J C CHARLTON

PERITONEAL SPLASH A PHYSICAL SIGN

SIR,—Mr F G Smiddy (Oct 15) points out that this physical sign can be elicited only in the anæsthetised patient Many years ago, when I saw more patients with perforated peptic ulcer than I do now, I noticed that in some it was possible to detect a splash while percussing for free gas in the peritoneal cavity Light and careful percussion in the line of the right nipple with the patient prone will in many cases reveal the gas bubble which obliterates the band of dullness over the liver At the lower edge of the bubble the pleximeter finger detects a faint splash as the abdominal wall comes into contact with the surface of the fluid behind the bubble This sign is easily elicited when the perforation is large, there is much effusion in the peritoneal cavity, and the rigidity of the abdominal wall is less than board-like But then the diagnosis can more confidently be made by other means In the early case with a small hole, little effusion, and a rigid abdominal wall the sign is not easily elicited

I concluded that as a physical sign it was of little value, but when present it provided a comforting confirmation of the diagnosis

Whiston Hospital,
Prescot, Lancs

J A MARTINEZ

SIDE-EFFECTS OF LIBRIUM

SIR,—I read with close attention the correspondence that followed the letter by Dr Ingram and Dr Timbury (Oct 1) about the new drug methaminodiazepoxide ('Librium')

My mind was certainly imbued with that attitude of scepticism and circumspection favoured by your correspondents when I first prescribed these capsules for patients with anxiety states, since I had seen in recent years the much-vaunted advent of a glut of new drugs, the great majority of which were destined to find ere long a dusty tomb on some neglected shelf of the dispensary I soon came to the conclusion, however, that librium is of much value in the anxiety states Considerable benefit was obtained in some 5 out of 10 sufferers from morbid anxiety, a result which was the more impressive because not a few of them had previously had little or no relief from other calmative drugs—which clearly mitigates the influence of suggestion A large majority of those responding to the drug need take the relatively modest dose of 10 mg three times daily to gain relief from their emotional tension, disagreeable side-effects being exceptional in such

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1 Gross J, Pitt Rivers R *Lancet* 1951, ii 766
2 Gross J, Pitt Rivers R *ibid* 1952 i 439
3 Gross J Pitt Rivers R *Biochem J* 1953, 53 645
4 Braasch J W Flock E V Albert A *Endocrinology* 1954 55, 768
5 Tata J R *Clin chim acta* 1959 4, 427
6 Gleason, G I *J biol Chem* 1955, 213 837
7 Rupp A F Beauchamp E E Farmakes J R United States Atomic Energy Commission document ORNL-1047 Production of Fission Product Iodine 131

circumstances Some of these patients remarked that, unlike other drugs they had tried, librium suppressed their anxiety without producing troublesome somnolence In my hands, the drug has proved more useful for the assuagement of diffuse anxiety than for the relief of the specific phobias of the obsessional neuroses

Although it would doubtless be prudent to postpone *final* judgment I am confident that this drug will soon win its spurs in general practice, and thereby materially reduce the number of cases of anxiety state referred to psychiatric out-patient clinics

Menston Hospital,
Ilkley, Yorks

J TODD

HEPATIC SIZE, SHAPE, AND CONTENT

SIR,—We must be grateful for having been reminded of the advantages of peritoneoscopy Though too seldom practised in this country, its value in the diagnosis of hepatic disease and anatomical abnormalities must be recognised

For the certain exclusion of disease, however, it is not so reliable, and this and its other limitations seem to me to indicate the desirability of laparotomy in determining that no hidden metastases are present in the liver

Churchill Hospital,
Headington, Oxford

C GRIMSHAW

NEGATIVE ASSOCIATION OF ABO BLOOD-GROUPS WITH FRACTURED HIP

SIR,—In your issue of Aug 13, Dr Wiener said that Buchwalter had observed an excess of blood-group A in patients with fractured femurs We note that Buchwalter [1] has investigated the ABO blood-group distribution in 910 cases of fractured hips and found no statistical difference when compared with a control group We have examined a small series of patients who had been treated for fractured femoral necks at this hospital All these patients had been blood-grouped on admission as a matter of routine

TABLE I—ABO BLOOD-GROUP DISTRIBUTION

Group	Control series	Intertrochanteric fracture group	Other femoral neck fractures	Total test series
A	1906 *(32.3%)*	56 *(42.8%)*	73 *(33.5%)*	129 *(37.0%)*
B	637 *(10.8%)*	9 *(6.9%)*	22 *(10.1%)*	31 *(8.9%)*
AB	178 *(3.0%)*	2 *(1.5%)*	6 *(2.7%)*	8 *(2.3%)*
O	3177 *(53.9%)*	64 *(48.8%)*	117 *(53.7%)*	181 *(51.8%)*
Total	5898	131	218	349

TABLE II—DISTRIBUTION OF THE RHESUS FACTOR

Rhesus	Control series	Fracture series
Positive	344 *(80.6%)*	279 *(79.9%)*
Negative	83 *(19.4%)*	70 *(20.1%)*
Total	427	349

Table I shows the ABO groups of these 349 patients and those of the control series compiled from data from 5898 consecutive new donor registrations with the West of Scotland Regional Blood Transfusion Service The patients were further subdivided into intertrochanteric fractures and other femoral neck fractures This small series reveals that there is no significant difference in ABO blood-group distribution, although one may be impressed by the relatively high incidence of group A in the intertrochanteric fracture group, there is no statistical difference ($\chi^2 = 1.3$) Furthermore, table II shows that there is again no significant difference in the incidence of the rhesus factor in the fracture patients and those of a small control series of 427 donors

We wish to thank Dr I A Cook, Mr W Sillar, and Dr J Wallace for assistance, and Dr R A Robb for his statistical help

Southern General Hospital
Glasgow

J MALCOLM CAMERON
A G MELROSE
G A WHITEFIELD

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[1] Buchwalter, J A *Acta genet* 1957, 6, 561

MODERN CLINICAL BIOCHEMISTRY

SIR,—Professor Cappell's presidential address (Oct 15) has called forth a prompt and explosive comment (Oct 29, p 985) from his biochemical colleague at the Western Infirmary

As a biochemist, Dr Hendry is naturally most concerned with Professor Cappell's assessment of the position of chemical pathology in the framework of clinical pathology, and there can be little doubt that he has voiced the feelings of many of the medical and non-medical biochemists who have entered or considered entering the hospital laboratory service These feelings are clearly expressed in their reluctance to apply for posts If Dr Hendry as the head of a teaching-hospital biochemistry department can say it is all but impossible to recruit young science graduates into hospital biochemistry departments, how much more so is this the case in regard to the non-teaching hospitals administered by regional boards, and this at a time when scientists are making fundamental contributions in every branch of industry and many other fields of activity Why should the hospital service alone be denied this advantage? Surely the health of the nation should have at least an equal call on the scientific potential No medical man can view this situation with equanimity, and least of all pathologists whose own work can gain so much more significance and value by close collaboration with chemical studies It would seem worth trying to find the explanation for the unpopularity of hospital work for science graduates

Firstly, the newly graduated chemist, if he is worth his salt, will wish to advance his knowledge and status by acquiring a postgraduate qualification This requires in the case of a PH D that the department in which he works will be recognised by a university department of chemistry or biochemistry as giving proper facilities for postgraduate study together with supervision by a senior member of the staff of these departments In the case of an M SC no university supervision is required, but unless the proper facilities are there the preparation of a thesis will be impossible These facilities consist above all in adequate time—and, in the case of more senior biochemists, assistance—to pursue a research project, and there seems no doubt that the greatest drawback to the hospital biochemistry service in the eyes of would-be graduate recruits is the lack of time and encouragement to undertake research Many pathologists consider biochemical research inappropriate in hospital laboratories, especially in non-teaching hospitals, or, even if they are convinced of its value, are unable to persuade hospital management committees to provide sufficient staff to enable the biochemical graduate to devote time to original investigations He is consequently inundated with routine and repetitive work and soon becomes dispirited and leaves the service, or stays on disgruntled with a grudge against doctors in general and pathologists in particular

No greater catastrophe could befall the pathologist than to lose that intimate contact with the biochemist which promises to solve many problems which neither can solve alone Yet it is clear from Dr Hendry's letter that the pathologists' laudable attempts to weld the hospital laboratory disciplines into a single integrated team are viewed with the greatest suspicion by medically and non-medically qualified biochemists alike The reason for this lies in the question of prospects The young biochemist is not going to sit back and vegetate when he has obtained his postgraduate qualifications He hopes eventually to attain as senior and respected a position in the hierarchy of the hospital staff as he would in industry or other Government scientific establishments, and to have a reasonable chance of running his own department Under the present circumstances he will find his way blocked in both these directions He cannot obtain status comparable with his medical colleagues as long as his method of appointment is that of registrars, technicians, and radiographers—viz , by hospital management committees and not by regional boards Neither can he obtain it—human nature being what it is—as long as his salary is so much less than that of his medical colleagues that he cannot join fully with them in social activities and educate his children similarly As for running his own department, it is generally believed that the Association of Clinical Pathologists considers that the biochemist should be directly responsible to the head of the laboratory in which he works (i e , the senior clinical pathologist), though I am not aware of any published statement of this policy While not suggesting that a non-medical biochemist should be in charge of the other clinical pathological laboratories, I am at a loss to see why a senior biochemist, whether medical or non-medical, should not be in absolute charge of his department, responsible only to the employing authority Of course there will be many matters of a clinical nature which he will want to discuss with the medical pathologists, but surely discussion on terms of parity is the essence of the teamwork which we wish to see in the integrated department of clinical pathology of the future

Yet another explanation for the mistrust by biochemists of pathologists lies in the manner in which the latter are organised for political purposes The Association of Clinical Pathologists has only medically qualified full members How can it be representative of biochemists in general ? If it wishes to be considered thus representative, it must give full membership to all hospital biochemists of suitable seniority (which would seem appropriate enough if hospital biochemistry is indeed a branch of clinical pathology !) Similarly if pathological advisory committees wish to be considered qualified to advise regional boards on biochemical matters they should admit senior non-medical biochemists to membership If these suggestions are not attractive to pathologists, would it not be better for them to leave the advising on biochemical matters to the Association of Clinical Biochemists on the one hand and to regional biochemistry advisory committees, still to be formed, on the other ? While retaining their role of principal advisor to the authorities on biochemical matters, these organisations would no doubt welcome and benefit by periodic discussions through joint consultative committees with the corresponding pathological bodies

In the meantime, the recruiting position has deteriorated to a stage where it is impossible to fill biochemical appointments even with candidates who are far from ideal There is here a vicious circle The poor quality of the majority of science graduates accepting posts in the hospital biochemistry service has prevented many pathologists from gaining insight into the reliability and potentialities of the best type of biochemist Otherwise it is possible that a far greater degree of responsibility and scope would have been accorded the science graduate Now it is too late, and in despair the pathologists have turned to the young men of their own profession to fill the gap Although there is much that is attractive in the medically qualified biochemist (chemical pathologist), the disadvantages would seem far to outweigh the advantages if he is only going to have one year of fundamental study in chemistry as Professor Cappell suggests With so little experience in chemistry, how will he be able to attract to work under him keen young scientists just leaving university departments of chemistry four years after they have taken their advanced level G C E ? If he does not attract them, the standing of our departments of chemical pathology will fall below those of departments of clinical chemistry in other countries

I would suggest it would be far more long-sighted to make the hospital biochemical service attractive to the best young brains in chemistry and biochemistry by introducing the following innovations

(a) Every biochemist post advertised (or at least a considerable proportion, which should be specially designated as largely free from routine and repetitive work) should carry with it (i) facilities for obtaining a postgraduate qualification, (ii) reasonable opportunity to reach status comparable in salary and independence with that of medical consultants,

(b) Research should be considered a normal and not an exceptional activity of biochemistry departments

(c) Appointments to senior (principal and top-grade) biochemical posts should be made by regional boards

(d) Biochemistry advisory committees should be appointed by regional boards and should always include a professor of chemistry or biochemistry

Although there are many other ways in which hospital biochemistry could be made more attractive, if those mentioned here are implemented there would surely be a most gratifying influx of the best type of scientist into the service, and I should like to see pathologists taking the lead in securing these improvements because it is they who will gain most by having the privilege of working as a team in close collaboration with the finest products of our universities' scientific departments

Midland Centre for Neurosurgery,
Smethwick

A L WOOLF

CHROMOSOME ANALYSIS

SIR,—I was surprised by Dr Stewart's letter of Sept 17 From his statements, one may conclude that colchicine and its derivatives causes heteroploidy and triploidy in animals So far as I am aware, the few cases of heteroploidy and triploidy observed in animals were associated with a highly artificial technique

Colchicine was added to sperm material and the animals artificially inseminated In this way, a few rabbits and one pig supposed to be triploids were obtained[1] [2] However, the accounts concerning these animals have been criticised and their triploid nature is unconvincing and not yet established[3] To sum up, it is apparent from these reports that no polyploid animals have been produced by colchicine[4] Moreover, colchicine does not cause gene mutation[5]

Recently, by intrauterine injections of colchicine into female mice just before mating, Edwards obtained some heteroploid embryos at 3½ days' gestation Chromosome counts of the mature offspring of these females, however, showed no heteroploids[6] Using a different technique, similar results were obtained in rats by French workers A few "heteroploid" embryos were seen at 12th day but none at full-term gestation[7]

The method is, I believe, simple and useful The results are good, and nothing suggests that the intravenous administration of the colchicine derivative is

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1 Melander Y *Hereditas* 1950 36 335 *ibid* 1951 37 298
2 Häggkvist, G Bane A *ibid* 1950 36 329
3 White M J D *Animal Cytology and Evolution* Cambridge, 1954
4 Eigsti O J Dustin P Jr Colchicine Iowa 1957
5 Dobzhansky T Genetics and the Origin of Species New York, 1941
6 Edwards R G *J exp Zool* 1958 137 317 *ibid* p 349
7 Piko, L., Bomsel Helmreich O *Nature Lond* 1960, 186 737

dangerous So far we have used the drug in 62 patients without any toxic manifestation

Department of Clinical Medicine,
Medical School of Ribeirao Preto,
Sao Paulo, Brazil

CÁSSIO BOTTURA

TREATMENT OF IDIOPATHIC HYPERCALCÆMIA OF INFANTS

SIR,—Many articles have now appeared about the treatment of idiopathic hypercalcæmia of infants A low calcium and vitamin-D intake, a high phytate intake, and the administration of cortisone have been recommended To my knowledge mention has not been made of the possible beneficial effect of total exclusion from ultraviolet rays

The antirachitic effect of sunlight is thought to be due to the activation of 7-dehydrocholesterol in skin This activation may result in the formation of substances with vitamin-D activity equivalent to 1000 or more units of vitamin D per day in infants who are exposed to ultraviolet radiation Possibly this disease has not been reported in Negroes because of the lesser effect of ultraviolet rays on deeply pigmented skin

It seems probable that infants with idiopathic hypercalcæmia are sensitive to very small amounts of vitamin D and it would seem advisable that patients with this disease be excluded from sunlight during those seasons when rays between 280 and 320 μ are present.

Possibly someone with knowledge of the metabolism of vitamin D might render judgment whether infants with idiopathic hypercalcæmia should be excluded from sunlight as part of their treatment

Department of Pediatrics,
Jefferson Medical College,
Philadelphia.

HANS G KEITEL

TREATMENT OF OBESITY BY THE HIGH-FAT DIET

SIR,—Bearing in mind case 5, and the large group of patients and friends she appears to represent, can Prof Yudkin and Miss Carey (Oct. 29) offer a 1500-calorie diet that is *permanently* acceptable both *socially* and financially to an adult woman of any age? An overweight woman is conspicuous in a crowd she does not wish to draw further attention to herself by always differing from the group when she is not eating alone

We would be most grateful

Hadleigh, Essex.

DAPHNE SASIENI

ERYTHROCYTE ENZYME DEFICIENCY IN UNEXPLAINED KERNICTERUS

SIR,—I was very interested by the contributions from Smith and Vella[1] and Doxiadis et al.[2] They confirm some observations I had the opportunity to report[3-6] last year

I have so far studied 19 jaundiced newborn children (11 males, 8 females) with unstable G S.H. and/or G -6-P D defect in their erythrocytes In 10 cases exchange transfusion was performed 7 of the transfused children and none of the untreated survived without damage Precipitating factors, such as dangerous drugs, were recognised in only a few cases Severe anæmia was rarely present, on the other hand, jaundice was often associated with severe clotting disturbances, indicating perhaps hepatic impairment, which may be due to the enzyme abnormality itself In fact, as I was able to demonstrate by liver biopsy, G -6-P D activity is decreased in the liver of sensitive individuals as well as in their erythrocytes[6] The observations of Smith and Vella and Doxiadis et al emphasise again the importance of this particular type of neonatal jaundice They also confirm the high incidence of the syndrome in a few families bearing the defect, and this fact suggests that there is a genetic factor in addition to the G -6-P D defect.

Clinica Pediatrica,
Università di Sassari,
Italy

FRANCO PANIZON

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[1] Smith, G Vella F *Lancet* 1960, i 1133

[2] Doxiadis S A, Fessas P Valaes T *ibid* July 2, 1960, p 44

[3] *Studi Sassaresi*, 1959 37 19

[4] *Acta pædiat latina*, 1959 12, 904

[5] XVII Congrès des Pédiatres de Langue Française, Oct. 1959, vol IV Montpelier

[6] *Boll Soc Ital Biolo Sper* 1960 36, 106

A SEVERE ANAPHYLACTOID REACTION TO HYDROCORTISONE

SIR,—Occasional allergic reactions following the local injection of hydrocortisone have been recorded,[1] and in many cases the possibility that associated use of hyaluronidase or procaine was to blame has not been firmly excluded The following case illustrates an allergic response of alarming severity to the injection of 'Hydrocortisyl' (Roussel) 5 ml in a patient who had never had either local or general steroid medication.

No other solution was injected and it was possible to exclude any previous injections (within 2 months) and any tablets or medicines (except 2 tab codein co *B P*, to which the patient was accustomed, taken a week previously) Similarly no dietary explanation could be discovered

A woman of 50 had, on April 8, 1960, a cup arthroplasty for osteoarthritis of the right hip She made a normal recovery, and was discharged to outpatients on June 17

On Sept 15, during follow-up examination, she complained of pain in the right shoulder A typical moderately severe supraspinatus tendinitis, with early pericapsulitis, was found, and at about 3.30 P M hydrocortisyl 5 ml was injected into the rotator cuff

She had no immediate ill effects, but at 7 30 P M, after supper, she suddenly felt her "face funny—blotchy with lumps, and burning" Red patches appeared on her arms, and she felt sick. She "passed out" and was carried to bed

An hour later, when her doctor arrived, she had regained consciousness, but she was vomiting profusely, had pain in the stomach and loins, and had urticaria, especially on the arms and face Conglomerate petechiæ and bruises appeared over the arms and face She was in a state of shock, with tachycardia, extrasystoles, and a weak pulse. There was much abdominal tenderness, especially in the liver area

She was given anti-histamines ('Piriton'), and she felt a bit better next day, but for 2 days she vomited repeatedly and had diarrhœa and rectal incontinence The stools were fluid and black, and the vomit contained dark blood

She was readmitted to hospital on the 3rd day Laboratory investigations showed hæmoglobin 92%, platelets 300,000 per c.mm, bleeding-time 2 min, clotting-time 6 min, clot retraction after 1 hour normal, prothrombin content 100% of normal, and prothrombin consumption normal The vomit contained dark blood, and occult blood was present in the stools The urine was normal.

Vomiting and diarrhœa ceased on the day of admission, and the abdominal pain and tenderness cleared up within 48 hours She returned home after 5 days

Although intradermal skin tests were unlikely to be helpful so soon after such a severe reaction, they were attempted on Sept. 7 using (1) control solution, (2) a minute dose of penicillin (to exclude penicillin contamination of the syringe used for injection), and (3) hydrocortisyl 0 01 ml An erythematous plaque 0 75 cm. in diameter formed in 24 hours around the site of hydrocortisyl injection, and persisted for 2 weeks, while the control sites showed no reaction

Thus it appears almost certain that this alarming reaction was due to the hydrocortisyl injection. Some

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[1] Kendall, P H. *Ann phys Med* 1958, 4, 170

2000 hydrocortisyl injections have been given in this department over the past 3 years, and except for one case of mild infection following an injection for tennis elbow no other ill effects have been encountered from the use of these injections for the minor orthopædic troubles treated by this method

My thanks are due to Dr Josef Grutz, who dealt with this emergency so capably, and who has cooperated in the inquiry concerning ætiological possibilities

Oldchurch Hospital,
Romford, Essex

R A KING

ZOLLINGER-ELLISON SYNDROME

SIR,—With great interest I read the article in your issue of July 16 concerning this syndrome with diarrhœa and malabsorption The gastric-secretion studies before and after removal of the pancreatic islet-cell tumour were particularly striking As the Birmingham group point out, confirmation of their observation with tumours of similar type is important, so you may be interested in the story of a patient Dr G J Verdonk and I reported[1] at a colloquium of gastroenterology in Antwerp in September, 1958

A 66-year-old woman who presented herself in June, 1957, had a continuous pain in the epigastrium, spreading to the back After meals the pain was worse and she complained of heartburn and eructation She had no diarrhœa—on the contrary there was a distinct constipation She never had hypoglycæmic attacks

Examination of this fat healthy-looking woman revealed a resistance in the left upper abdomen which was at first thought to be an enlarged spleen

Erythrocyte-sedimentation rate 15 mm in one hour Hæmoglobin 12 8 g per 100 ml White cells 5400 per c mm, normal differential count Liver-function test normal No occult blood in the fæces Urine normal A fractional test-meal showed considerable hyperacidity free acid 106, total acid 120

X-ray examination of the stomach did not demonstrate an ulcer, but the mucous-membrane pattern was rough On compression of the stomach an area of lack of contrast was visible, possibly caused by pressure from behind The radiologist suggested a pancreatic tumour or cyst Just distal to the duodenal bulb a pseudopodial contour was seen, interpreted as a diverticulum

After six weeks' ulcer treatment with rest, diet, antispasmodics, sedatives, and antacids she was admitted to hospital, because the abdominal mass was still palpable We finally decided on operation On Nov 1, 1957, a pancreatic tumour, 7×6 5×6 5 cm, was removed During the operation the stomach and intestines could not be explored The surroundings of the tumour and omentum were hyperæmic and contained large dilated veins The omentum was containing the tumour and was firmly connected to the surface of the spleen The tumour was removed without vagtomy or gastrectomy The histological diagnosis was " insulinoma "

In September, 1958, nearly ten months after the operation, a fractional test-meal showed that the acid secretion was now reduced to subnormal free acid 0, total acid 16 (maximum)

Municipal Hospital,
Arnhem, Holland

M DIJK

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[1] Dijk, M, Verdonk G J *Tijdschr Gastro enterologie*, 1958, 1, 481

The Widdicombe File

LXVII —THE DIVISION OF PATHOLOGISTS

DEAR PETER,

I too thought your letter was sound but I think your friend G G, like several of the pathologists, is not entirely familiar with the real function of a college They ask " Can we trust the physicians ", meaning presumably the internists, the dermatologists, the pædiatricians, the neurologists, the psychiatrists, and the other *clinicians* in the college, and they talk earnestly about the need for independence But, bless our souls, why do they need to be independent? A college is basically a degree-granting body and also ideally a community of individuals with kindred interests Do we hesitate to take a university medical degree because we doubt the good intentions of the philosophers or theologists who are represented in its court, or do we demand independence so as not to have to eat at table with engineers or lawyers? Maybe the young men want independence at any price because this is the parrot cry of the mid 20th century Fortunately in the college the dermatologists seem to show no distrust of the psychiatrists, and the neurologists are not afraid of being outvoted by the general physicians else there would have to be lots of new colleges What will it benefit the pathologists of tomorrow to have their own college with its expensive library and regalia, portraits and plate? Are pathologists anxious to accept the social and other obligations of a college and to maintain an expensive establishment—for rest assured they will not for long remain content with an attic in Euston but will feel the urge to compete on the perimeter of Regents Park?

Although your arguments were sound one correspondent accused you of talking nonsense His letter reveals the lack of cohesion amongst pathologists and indeed the seed of the next potential split (" Can we consultant biochemists trust the pathologists and bacteriologists?—we must be independent at all costs ") What I mean is this, Peter, if the pathologists (and I am using this term generally to include bacteriologists, virologists, chemical pathologists, serologists, forensic pathologists, and hæmatologists—all in fact who are concerned with the laboratory investigation of the patient alive or dead) do not accept this very generous offer of negotiation by the Royal College of Physicians (some claim that it will fail because it is too generous), they may have to wait a long time before achieving the unanimity they require to embark on a new venture Many of the academic pathologists—if what I hear is true—care little whether there is a faculty of the college or a new college

Please impress on your many pathologist friends, Peter, that a faculty will require an appreciable measure of support but a new college will require overwhelming support from all species of pathologists Remind them that a faculty can always be dissolved (I trust that in the event of a faculty both the pathologists and the college will insist on having this in their agreement) but once they embark on a college they will have committed their successors to a life of independence and will have severed connection with their clinical colleagues A recent president of the college, it is said, once invited the pathologists to look forward fifty years They should do this now The rapid growth of specialism, automation, and the increasing excellence of technicians may bring the pathologist of the future much nearer to the patient than he is today and nearer to the clinicians An irrevocable move at this time would be a misfortune

Yours ever,
W W

Parliament

Queen's Speech

In the Speech from the Throne at the opening of Parliament on Nov. 1 it was announced that the Government proposed to increase war pensions, and retirement pensions, other benefits, and contributions under the National Insurance schemes.[*] They would authorise an increasing level of expenditure on the physical recreation of the young. Awards for students at universities and for those taking comparable courses at other institutions of higher education would be granted on an improved basis. They would introduce a Bill to provide better means of dealing with young offenders, to extend compulsory after-care to prisoners and so to discourage them from reverting to crime, and to improve the management of approved schools.[†]

Welsh Teaching Hospital

On Nov. 2, on the adjournment, Mr LEO ABSE sharply criticised the plans for this new teaching hospital, which he described as an "ossified hospital design accepted from a septuagenarian architect by assessors led by another septuagenarian architect ... a design for a hospital for 1950, not as it should be for a 1980 hospital." Wales wanted a forward-looking teaching hospital, it was being proffered a mausoleum.

Going on to offer detailed criticisms, he said that the contemptuous attitude to research was well illustrated by the location and space allocated to the animal house. In defiance of hospital planning, the X-ray department was so embedded within the building that expansion was well nigh impossible. A derisory amount of space was allocated for radioisotopes. A trivial 32 beds had been allocated to mental illness, and there was still no sign of a department and chair in psychiatry being created. But the most dismaying feature was the ludicrous amount of space allocated for research in relation to bed space. The design gave every appearance of there having been a battle for beds between heads of departments.

Other points which he made were: quiet rooms in the noisiest part of the building, the sluice room farthest from the beds most needing its services and unrelated to treatment suite, cross-infection risks increased by infected material being brought into the ward suite for disposal and by inadequate air-conditioning, lavatories concentrated in blocks and not related to bed areas or day spaces, an operating-theatre with a wood-block floor which could never be sluiced clean, eight-storey light wells which meant that wards would be badly lit and have a wretched outlook.

All these blunders and many more, he added, would be housed in a dull cliff-like bulk of buildings unmistakably institutional in appearance.

Miss EDITH PITT, the parliamentary secretary to the Ministry of Health, welcomed the opportunity of discussing the University Hospital of Wales and of replying to some of the criticisms. The fact that it was an undergraduate medical school dictated not only the concept of the work to be performed there but also the site of the hospital, which was to have 650 beds. The scheme must be viewed against the development of acute hospital services in South Wales, which included not only another major acute regional hospital working in the Cardiff area but also major acute hospitals at Bridgend, Pontypridd, and Newport, and others in the Welsh Hospital Board's plans for Merthyr and North Monmouthshire.

The Board of Governors of the United Cardiff Hospitals and the Welsh National School of Medicine desired a hospital integrated with a medical school, with the closest possible working arrangements between the professional and the clinical staff and with the various departments and their research and other laboratories. An architectural competition for an important scheme of this size was thought preferable to selecting an architect, because it was believed that competition would give incentive to a number of architects to think about the problems set by the promoters and that new ideas and techniques might be evolved. Competition, however, could do no more than select an architect and, in a scheme of this size, a fundamental design. The promoters and architect could deal with each other on paper only in broad outline. The details must wait till later. A series of working parties had now been set up to go into the plans of the various units with the architect and with the engineer.

Ward units, outpatient department, lifts and communications, catering and food distribution, training accommodation, the dental school, were all being looked at in this way. The internal design and layout of the ward unit, for instance, had already been replanned to provide better access and better supervision; to take account of the latest thoughts on cross-infection, more single rooms had been provided, and the large ten-bed unit had been broken up into smaller units.

This was a normal process which one would expect to take place with any design, and similar replanning was going on throughout the hospital. The promoters had examined the design carefully in the light of the numerous criticisms and were satisfied that the completion of the process of preparation of detailed sketch plans, which was now going on, would give them a modern and efficient hospital and a medical teaching centre. She thought it premature at this stage to be too critical of the detailed planning because the details had still to be filled in. It was her earnest hope that, when this hospital was completed, the Welsh people would have a hospital in accordance with their wishes and a hospital of which they might be proud.

QUESTION TIME

Poliomyelitis Vaccination

At Sept. 30, 13,333,000 people in England and Wales had been vaccinated against poliomyelitis under the National Health Service.

Appointments

BIRKBECK, M. Q., M.B. Cantab., D.PHYS.MED.: consultant in physical medicine, Northampton Kettering area.
BROWNE, M. P., M.B.E., M.B. N.U.I., D.T.M. & H.: airport M.O., health control unit, London Airport.
BURTLES, RICHARD, M.B. Lond., F.F.A. R.C.S.: consultant anæsthetist, Northampton and Kettering area.
EMERY, RALPH, M.B. Lond., M.R.C.P.E., D.P.M.: assistant psychiatrist (S.H.M.O.), Aylesbury and High Wycombe area.
ETON, BRUCE, M.D. Manc., M.R.C.O.G.: S.H.M.O., maternity hospital, Cambridge.
LUNN, J. E., M.B. Glasg., D.P.H., D.P.A.: assistant M.O.H. and assistant school M.O., Oldham.
ORTON, W. T., M.B. Belf., D.P.H.: senior assistant M.O., Wembley and Willesden.

Birmingham Regional Hospital Board

BATTEN, R. L., F.R.C.S.: consultant surgeon, West Bromwich group of hospitals.
GALLA, THOMAS, M.B. Edin., D.P.M.: consultant and deputy medical superintendent, St. Edward's Hospital, Cheddleton, and Stoke-on-Trent hospital group.
HILL, EILEEN E., M.D. Glasg., M.R.C.P., D.C.H.: consultant pædiatrician, Birmingham (Selly Oak) hospital group.
ROSS, H. P., M.B. Aberd., D.P.M.: consultant psychiatrist and deputy medical superintendent, Lea Hospital and Lea Castle Hospital.
ROSS, J. H., M.D. Cantab., M.R.C.P., D.OBST.: part-time consultant physician, Herefordshire hospital group.
SAGE, R. H., M.B. Birm., F.R.C.S.: consultant surgeon, Birmingham (Selly Oak) hospital group.

Liverpool Regional Hospital Board

OSWALD, D. C., M.B. Dubl.: assistant pathologist, Birkenhead H.M.C.
PORTER, R. A., M.B. Belf.: deputy medical superintendent (S.H.M.O.), Moss Side Hospital.
SNOW, R. G., M.B. Birm., F.F.A. R.C.S.: part-time consultant anæsthetist, Chester area.

Manchester Regional Hospital Board

FLEMING, A. C., M.B. Durh., D.P.M.: consultant psychiatrist and medical superintendent, Calderstones Hospital, Whalley, near Blackburn.
GRIMSHAW, LINTON, D.F.C., M.B. Manc., D.P.M.: consultant psychiatrist, Bury and Rossendale hospital group.
KRAWIECKI, J. A., M.B. Edin., D.P.M.: consultant psychiatrist, West Manchester and Springfield and Swinton hospital group.
METCALFE, W. J., M.B. Manc., F.R.C.S.: consultant surgeon, Blackburn and district hospital group.
SIMPSON, D. C., M.B. Edin.: senior casualty officer, Withington Hospital, near Manchester.

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[*] Details of these proposals are given on p. 1081.
[†] Details of these proposals are given on p. 1082.

Obituary

JAMES ERIC PATERSON

M B Glasg , F R F P S

Mr J E Paterson, honorary consultant in neurosurgery to the Scottish Western Regional Hospital Board, died at his home in Rothesay on Oct 26

He was the son of a doctor and graduated from Glasgow University in 1911 as the most distinguished student of his year He spent some years in resident hospital posts, in general practice, and in junior staff appointments in surgery, gynæcology, and anæsthetics before he joined the R A M C to serve in France during the first world war After the war he returned to general practice and part-time specialism, and in 1920 was elected F R F P S

In 1926 he was offered the post of visiting surgeon to Stobhill Hospital, Glasgow, at that time a poor-law institution with 2000 beds for the aged and the chronic sick This appointment required him to give up general practice but gave him no chance to build up a consulting practice, and its acceptance meant a considerable financial loss A colleague relates

" To be poorly paid for tending the ' dregs of humanity ' was no deterrent to this extraordinary little man From the apparent dross he extracted much gold and gained a breadth of experience which few have achieved To suit his poor-risk patients he developed multi-stage operations He quickly learned the need for meticulous preoperative preparation and postoperative care and set up a specialised anæsthetic service In the early '30s his was a lone voice preaching the gospel of biochemistry, and he used the, then, slight resources of that science to the full Blood-transfusions were commonplace in his work when they were seldom thought of elsewhere, and before the late war there was a blood-bank in Stobhill

" He was indeed a general surgeon, whose work ranged from the newborn to the geriatric patient and embraced all specialties His technique was superb Watching him operate was like turning the pages of a beautifully illustrated atlas of operative surgery The neat, the precise, the anatomical attracted him, and he derived much pleasure from his practice of abdominal and reconstructive surgery and from urology, but neurosurgery became his true love This specialty he developed step by step from zero, beginning with attempts to relieve the hopeless cases admitted to Stobhill for terminal care In less than ten years he changed his wards from what was derisively called the ' deid hoose ' to a teaching unit "

The worth of Paterson's work in neurosurgery was soon recognised, and he was appointed neurosurgeon to the Victoria Infirmary He continued to work there until the establishment of the neurosurgical unit at Killearn in 1940 When the National Health Service was started, he gave up general surgery—not without much heart-searching—and confined himself to neurosurgery

E A T , once one of his students, writes

" Two things were noteworthy about Eric Paterson The first was that he was a great man With the cultivation of a new specialty he combined modesty, enthusiasm, unmitigated frankness about himself even more than about others, unvarying truthfulness, and an uncanny habit of being right in his judgments These are not the qualities which produce an overblown reputation during a man's lifetime, but they indicate the second noteworthy feature about him, which was that his greatness was not as widely known as might have been expected Instead he built a solid foundation of friendship, respect, and those ultimates in admiration—emulation and imitation He threw away opportunities to be grandiose, he gave limelight to juniors, and he demanded no ceremony Such attributes are looked back on after years with love Even his faults were venial, for though his irascibility towards foolishness was legendary he was never hurtful His influence will outlast more brittle reputations Nor for generations will the personal magnetism of the man fade from the minds of his pupils, and his pupils' pupils for even longer the traditions of the units they serve must reflect the imprint of his character "

S A sends a physician's tribute

" Wee Pat was really known and understood by only the surgeons This was entirely proper He belonged to them Maybe physicians—second to none in their admiration for him —like to imagine this frail little man cast in a different role To them it seemed strange that a surgeon should flit through the world on tiptoe—eager, tireless, and radiant His face—specs and all—was a classic for the students sensitive to the physiognomy of intellect Few men revealed in their demeanour, voice, and gesture so vivid a spectrum of human emotions the tranquillity of deep meditation, the turbulence of the exploring mind, the flash of anger, and the smoulder of despair But most memorable of all was his dazzling smile—impish and mischievous—transforming the senior surgeon into a jubilant schoolboy, but eloquent too of his deep humanity James Eric was splendidly endowed with the attributes shared by the artist and the philosopher-surgeon he was in love with the world of beauty; and its glory and splendour were reflected in his imagination Out of these his riches he gave abundantly to patient and colleague alike they rejoice in his talents, they grew and were fortified by his example "

W G also writes of the man as well as of the surgeon

" Wee Pat's knowledge of surgical literature was immense, but surgery by no means filled his life He regarded the world with childlike wonder so that all things were of interest to him In literature, poetry, biography, music, and philosophy he was astonishingly well informed Botany and geology were his delight Sailing was a pleasure with him till it became too strenuous for his years, and then he turned to painting Critical as he was of his own efforts here, he developed his not inconsiderable talents to the full by his customary intense application Because of all his interests he was self-contained, and boredom was unknown to him, but he loved to meet a fellow enthusiast and made many friends through his hobbies

" In his earlier years his sensitivity and his enthusiasm made him a little prickly and intolerant, but the passage of time wore away the sharp edges and left a benign, mature personality as stimulating as ever He had no ambition to order other people's lives, and as a committee man he was a self-confessed failure He could not tolerate scheming and lobbying

" When he retired many groups of friends and associates gave him dinners and presentations The Wee Man was deeply touched and quite bewildered by these tokens His modesty had never allowed him to guess his own greatness nor to realise that he had gained ' that which should accompany old age, as honour, love, obedience, troops of friends ' "

Mr Paterson leaves a widow and two sons, one of whom is in general practice at Forres

Mr C W KIMBELL

G C S writes

" It was in the unpleasant circumstances of the 1940 campaign and then in captivity that Kim's sterling quality of character showed itself in all its brilliant clarity His devoted care of the wounded prisoners and his unswerving loyalty to those who served with him were an inspiration to all Small wonder that he had a host of friends who remember with affection and admiration his generosity and kindliness and his inimitable conspiratorial chuckle To all those the world is now a colder place "

Notes and News

WORLD HEALTH ORGANISATION

AT a meeting in Geneva of the W H O Executive Board, which opened on Oct 25,[1] Dr V Butrov (U S S R) stated that the U S S R would give 2 million roubles in 1961, in addition to its previous contribution, to the malaria eradication special account The Board decided to recommend to the next World Health Assembly that part of the cost of the malaria eradication programme should be financed from the regular budget The Board recommended a supplementary budget for 1961 of $800,000 This includes $100,000 for W H O assistance to the Congo, a further $2,700,000 for the same purpose will be provided by the United Nations

The Board commended Dr M G Candau, the Director General of W H O, for the promptness and efficiency of W H O assistance, and requested that it should continue They also thanked the International Committee of the Red Cross, the League of Red Cross Societies, and Governments which had helped with the emergency health programme

MENTAL ILLNESS IN SCOTLAND

AT the end of 1959[2] the total number of people in Scotland who were under care for mental illness was 20,682 (467 fewer than at the end of 1958) Of those in mental hospitals (including the State Mental Hospital at Carstairs) 14,022 were certified patients (922 fewer than at the end of 1958) and 6385 were voluntary patients (472 more than at the end of 1958) The number of admissions (excluding transfers) during 1959 was 12,428 (990 more than in 1958) Admissions of voluntary patients increased by 1175 to 9977 (80% of the total), but admissions of certified patients dropped by 188 to 2451 8719 voluntary patients (1095 more than in 1958) left hospital during the year Discharges of certified patients (including discharges " by escape ") numbered 1935 (118 more than in 1958) of whom about two-thirds were classified as ' recovered "

At the end of 1959, the total number of certified mental defectives was 8421 (98 more than at the end of 1958) Of these 5107 were in institutions and 2466 under guardianship Admissions of certified defectives to institutions during 1959 numbered 445 (53 more than in 1958) 234 patients were also admitted on an informal basis and 29 patients were transferred from certified to informal status The number placed under guardianship was 111 (8 fewer than in 1958) 215 were discharged from compulsory detention (including those discharged " by escape ")

A special study of readmissions during 1959 showed that of all admissions during the year 4480 (36%) were of patients with a previous admission 1139 were readmitted within three months of last discharge, 886 (7%) within six months, 624 within nine months, and 365 within a year

A NOVEL CLINICAL TRIAL

THE ethics of clinical trials can raise heated discussions wherever doctors meet, whether in lecture hall, laboratory, operating-theatre, hospital common-room, or students' hostel Now, perhaps because his pseudonym covers a man with an F R C S, Mr John Rowan Wilson has made a medical version of the dilemma of means and ends the centre of his novel, *Double Blind*[3]

A young bacteriologist is carrying out on a tropical island a double-blind trial with a vaccine against a form of encephalitis The trial is being financed by a German drug firm which hopes to patent part of the manufacturing process The island is an isolated primitive community under the tutelage of the Colonial Office In obtaining permission to carry out the trial in its hospitals and clinics official channels have been by-passed Though the natives normally give their permission before receiving the vaccine, it is unlikely that they realise the significance of the request On the other hand, " South Atlantic " encephalitis is an endemic and dangerous infection and its control would be an enormous benefit to the community Two deaths occur which may or may not be due to the vaccine A Catholic priest complains The Colonial Office, uneasily aware of lapses in protocol, if not in morality, send out a doctor to report on the trial

This complex epidemiological situation contains many of the important issues which beset the conscience of the research worker It is further complicated by the tense personal relations of the doctor, the bacteriologist, and his wife Their personal problems are solved by the novelist's manipulation of the plot The questions of general principle inevitably remain unsolved, but it is to their intelligent presentation that the book owes much of its unusual interest

BIOLOGICAL ENGINEERING SOCIETY

THE first scientific meeting of this society was held on Oct 15 at the National Institute for Medical Research, Mill Hill In his opening address, Sir Charles Harington drew a parallel between the state of biological engineering today and biochemistry half a century ago Perhaps in the years to come, he said, a fusion of the two disciplines of biology and engineering might result in biological engineering becoming as acceptable as biochemistry today In the meantime, advances in biological and medical science depended greatly on advances in engineering and instrumentation, and the society was making a valuable contribution by enabling biologists and engineers to work more closely together Prof R F Woolmer, the president of the society, thought it appropriate that this first meeting should be held at the Institute, for its work and organisation was a good example of the way in which engineers could work together with biologists About 100 people attended the meeting, and the programme of demonstrations was planned to give a cross-section of the subjects which the society hopes to cover

SPASTIC SCHOOL-LEAVERS

ONE of the most useful qualities of voluntary organisations is their refusal to leave fairly well alone The British Council for the Welfare of Spastics, now that they are satisfied that there is no longer a general shortage of school places for spastics, have turned their attention to the difficulties which these young people face when they go out into the world[1] A pilot survey made by the council gives a depressing picture

> Of 34 recent school-leavers only 9 were thought to be capable of becoming fully self-supporting Though 7 of these were in work only 3 were in jobs with reasonable prospects None had received any training Another group of 16 were described as ' doubtfully employable , and of these 5 were in jobs and 5 awaiting training None are ever likely to become financially independent The remaining 9 were expected to be unemployable

Thus, in all, only 12 were employed and not in very satisfactory jobs The highest wage earned was £5 10*s*, and even those of average intelligence were doing work well below their capabilities Of the 22 who are not in jobs some are in institutions or awaiting admission Others live at home and some attend occupation centres Some are waiting for training All are thoroughly under-occupied and lack enough interests to fill their days, and this leads to mental and physical deterioration In or out of jobs, they seem to lack friends and social life Clubs for the handicapped do not attract them, for whether practicable or not, they want to go out to work like other youngsters They seem to lack realism about their capabilities and of standards in the outside world, perhaps because of the inevitably sheltered atmosphere of the schools in which they were educated

The numbers in the survey are small, and the Council offer the results not as a basis for recommendations but as evidence of need. The results are a salutary reminder that, like the rest of us, the handicapped are living longer and that the support we give them must be continuous and flexible, keeping pace with their changing ages and circumstances

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[1] See *Lancet* Nov 5, 1960, p 1037

[2] Report of General Board of Control for Scotland for the year 1959 H M Stationery Office Cmnd 1160 1960 Pp 33 2*s* 6*d*

[3] The Double Blind JOHN ROWAN WILSON London Collins 1960 Pp 256 16*s*

[1] Annual report 1959-60 The address of the Council is 13, Suffolk Street, Haymarket London S W 1

University of Cambridge

On Oct 29 the following degrees were conferred

M D—P A J Ball J H Cule, P C Gautier Smith, J C Kelsey, C G Rob (by proxy), David Wise
M B—T J Willis

University of Birmingham

Dr R L Edwards has been appointed senior lecturer and first assistant in the department of obstetrics and gynæcology

University of Glasgow

On Nov 5 the degree of M D was conferred on William Cullen (with commendation) and on Joseph Sluglett

University of Queensland

Dr T J Rendle-Short, lecturer in child health in the University of Sheffield, has been appointed to the newly established chair of child health in this university

Royal College of Physicians of London

Dr K D Keele will give the FitzPatrick lectures on Tuesday, Nov 29, and Thursday, Dec 1, at 5 P M, at the college, Pall Mall East, S W 1 His subject will be Evolution of Clinical Methods in Medicine

Royal College of Physicians of Edinburgh

A meeting of college was held on Nov 1, with Dr A Rae Gilchrist, the president, in the chair

A Hill Pattison-Struthers bursary for 1960 has been awarded to Dr Philip Lanzkowsky and the Jean Hunter prize for 1960 to Dr A W E Soysa

The following were elected to the fellowship

Eric James M M Whittet, Keshavarao Krishnarao Datey, H G H Richards, H R L Fraser, A B Hegarty, J S Robson, J A Loraine, Tadepalli Shamsunder Row, R C Jackson, Velva Schrire Agnes L Scott, B C Sinclair-Smith, A C Kennedy, John Butler, K L Stuart, Arthur Jarrett A R Somner D S Nand, S L A Manuwa, J H Hutchison, D F Cappell, J H Walters, K W Donald, A W Woodruff, Eric Samuel

The following were elected to the membership

C W Kidd, A P Meiklejohn, R M Vanreenen, Krishna Rao Purohit, H L Davis R W McConnachie, Thambippillai Vamadevan, A R Adams, N R Young William McQuaker Sean O Reilly, L H Harris D G B Powell, David Jacobson, Elaine M Belton, Ralph Emery, J K Binns, Sheikh Muhammad Haneef, Ram Singh, G C Timbury, Joseph Gatt Barry Lewis, Anand Mohan Sur, R G B Williamson, Hamdy Mahmoud El-Sayed, Samir Mohamed Omar Hilal, Mookencherry Cherian Mathews, A I Rae Frank Tsu Chang Hu David Burrows, Nedumchalil Markose Mathai Baboobhai Rambhai Patel B S David Achyut Govind Motiwale, Peter Taylor, N P Burns, Kishin Hingorani, J D Woolridge, Boon-Kheng Khoo, I R Lawson Pandramajal Narayanappa Krishnamurthy Khalid Haji Aboo Mitha Nalkundad Kyathappanavara Channappa, R A Osborn, Dona Priyalatha Wijesinghe, M D Bowie, Lotfy Labib Basta, Vishnukumar Gupta Erasmus Lynghdoh, M G Dunnigan, Iain Michie, Harischandra Ranasinghe, Ekpo Edet Eyo, Chenniah Javarayya Bhakta Ram, Krishnadhan Datta, Susil Chandra Munsi Subrata Sen, Cheruvcetil Kochukutty Gopi Mohammad Ata, J A Waddell, Bhim Sen Ghisaram Singhal, Chandidas Gupta, Joseph Levin, E S Garnett, Gulamabbas Juma Ebrahim, W H S George, J A McBride

Heberden Society

Dr J J Bunim will give a Heberden oration on Friday, Dec 2, at 4 15 P M, at the Wellcome Foundation, Euston Road, London, N W 1 His subject will be a Broadened Spectrum of Sjögren's Syndrome and its Pathogenetic Implications

North West Metropolitan Regional Hospital Board

Lord Moynihan has been appointed chairman of this board

Albert Lasker Grants

The American Public Health Association have awarded grants to Dr F H C Crick, of Cambridge, and Dr M H F Wilkins, of London, for their work on processes governing heredity in living cells and viruses, and to Prof Lionel Penrose for his contribution to the development of human genetics and his findings on the effect of nuclear and other radiation on human beings and their offspring

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On Wednesday, Nov 16, at 5 15 P M, at the Royal Free Hospital, Gray s Inn Road, London, W C 1, Sir William Morrow, physician to the Royal Prince Alfred Hospital, Sydney, will speak on ulcerative colitis

Applications are invited for grants for research into diabetes mellitus and associated diseases Further particulars may be had from the secretary of the research grants committee of the Association, 152, Harley Street, London, W 1

Diary of the Week

NOV 13 TO 19

Monday 14th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
4 P M Dr Brian Ackner *Depressive Illness—Clinical Syndrome and Treatment*
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 P M Dr P D Samman *Eccrine and Apocrine Glands in Health and Disease*

Tuesday, 15th

UNIVERSITY COLLEGE, Gower Street, W C 1
5 30 P M Prof J H Gaddum Pharmacological Analysis of Tissue Extracts
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr K S Kirby Nucleic Acids and Cancer
INSTITUTE OF OBSTETRICS
3 P M (Hammersmith Hospital) Dr Helen Payling Wright *Varicose Veins in Pregnancy*
ST MARY S HOSPITAL MEDICAL SCHOOL W 2
5 P M (Wright Fleming Institute) Prof Norman Morris Human Relations in Obstetrics
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Mr G C Knight *Trigeminal neuralgia*
ROYAL ARMY MEDICAL COLLEGE, Millbank, S W 1
5 P M Dr Wilson, F INST P Nuclear Physics
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M (General Infirmary at Leeds) Dr Bertram Selverstone (Boston) Modern Treatment of Gliomas
MANCHESTER MEDICAL SOCIETY
4 30 P M (Medical School, University of Manchester) *Medicine* Dr J J Bunim (Bethesda) Alkaptonuria and Ochronosis

Wednesday, 16th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Dr A L Greenbaum *Fat Metabolism*
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Clefts, Vesicles, and Bullæ
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr J N Pattinson Abnormalities of the Mediastinum
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 15 P M *General Practice* Dr G I Watson, Dr Samuel Leff, Prof C H Stuart Harris Infectious Diseases Today
HARVEIAN SOCIETY
8 15 P M (Joint meeting with the Osler Club at 11, Chandos Street W 1) Dr A White Franklin, Dr Maurice Long, Dr T F Cotton, Sir Geoffrey Keynes, Mr A Dickson Wright Harvey and Osler
UNIVERSITY OF LEEDS
5 P M (General Infirmary at Leeds) Mr G W Theobald Gynæcological Pain
6 P M Mr J B Farquhar Third State of Labour

Thursday, 17th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P M Prof D V Hubble The Endocrine Orchestra (Langdon Brown lecture)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Dr J C Kendrew The Structure of Proteins
BRITISH INSTITUTE OF RADIOLOGY, 32 Welbeck Street W 1
8 P M Mr J B Massey Mrs J J Gough Dr Walter Shanks Dr A M Jelliffe Role of Moving Field Techniques in Treatment with High Energy Radiation
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield Morris Orthopædic Hospital, Oxford
8 30 P M Mr J Crawford Adams Ischio Femoral Arthrodesis for Osteoarthritis and Tuberculous Arthritis of the Hip
MANCHESTER MEDICAL SOCIETY
8 P M Sir Robert Macintosh A Trip to Russia and China
HONYMAN GILLESPIE LECTURE
5 P M (University New Buildings, Teviot Place, Edinburgh) Prof T N A Jeffcoate Functional Disorders of the Female Bladder and Urethra
UNIVERSITY OF ST ANDREWS
5 P M (Physiology Department, Queen s College Dundee) Mr L N Pyrah *Use of the Loops of Small and Large Intestine in Urological Surgery*

Friday, 18th

UNIVERSITY OF LONDON
5 30 P M (University College) Prof M Westergaard (Copenhagen) *Some Fundamental Concepts and Problems in Molecular Genetics*
ROYAL SOCIETY OF MEDICINE
5 30 P M *Epidemiology and Preventive Medicine* Dr E R Hargreaves Epidemiological Studies in Cornwall
ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATIO
2 15 P M (1 Wimpole Street, W 1) Dr Eliot Slater Hysteria 311 (Maudsley lecture)
POSTGRADUATE MEDICAL SCHOOL OF LONDO
10 A.M Mr H Osmond Clarke Cervical Disc Lesions
4 P M Prof C E Dent Primary Hyperparathyroidism
FACULTY OF RADIOLOGISTS 47 Lincoln's Inn Fields, W C 2
4 30 P M Prof R W Scarff Prognosis in Carcinoma of the Breast (Skinner lecture)
PLYMOUTH MEDICAL SOCIETY
8 30 P M (North Friary House) Dr Richard Asher See How They Come

Saturday, 19th

COLLEGE OF GENERAL PRACTITIONERS
11 30 A M (B M A House W C 1) D *Lindsey Batten* The Medical Adviser (James Mackenzie lecture)

The Lancet · Saturday 19 November 1960

DISEASES OF THE BASAL GANGLIA

THEIR RELATION TO DISORDERS OF MOVEMENT*

D. Denny-Brown
O.B.E., M.D. N.Z., D.Phil. Oxon., LL.D. (hon.), F.R.C.P.
PUTNAM PROFESSOR OF NEUROLOGY,
HARVARD MEDICAL SCHOOL, BOSTON, MASS.

I

The term basal ganglia has no precise limitation, having been used by the older anatomists for the large grey masses at the base of the brain, including the optic thalamus. In the present century the thalamus has been excluded, and the use of term limited to the caudate nucleus, the putamen, and the globus pallidus. For neuropathological reasons certain closely related subthalamic nuclei are often included. I shall not here discuss the intricate, and in part disputed, interconnection between these structures. The most important of these are shown diagrammatically in fig. 1, which is designed to emphasise the reflex pathway from the intralaminar (I L) and centrum medianum (C M) nuclei of the thalamus to the globus pallidus, putamen, and caudate nucleus, and the efferent connections of these nuclei with the subthalamic nucleus (S), the reticular formation of the midbrain (M B R), and the substantia nigra (S N). Short pathways connect these scattered subthalamic structures with the important motor reticular formation of the brainstem. The caudate nucleus, putamen, and globus pallidus also receive pathways from various areas of cerebral cortex. The caudate nucleus contributes an important pathway to the lateral thalamus. Though the basal ganglia are closely interrelated with the cerebral cortex in this way, they preserve both structure and function in its absence. This independent reflex activity is responsible for much of the behaviour that distinguishes the decorticate from the decerebrate animal.

My first objective is to define the degree to which diseases affecting the different ganglia produce consistent physical signs. Before 1895 there was no hint that damage to this region of the brain had any specific effect, though in the time of Hughlings Jackson it was customary to regard the basal ganglia as the seat of regulation of those simple spasms that remain when the cerebral cortex is destroyed. The first hint that specific disorders of movement are related to limited disease of these ganglia appears to have been the excellent description of congenital double athetosis by Anton in 1896, with the related scarring of the outer putamen on both sides. The most convincing demonstration, however, was the description of progressive lenticular degeneration by Kinnier Wilson (1912), providing a dramatic demonstration of the relation of limited lesions of these ganglia to rigidity, distorted posture, and tremor. Only then did the earlier descriptions of outfall of nerve-cells in the globus pallidus in paralysis agitans by Jelgersma (1908), and the comparable atrophy of the caudate nucleus in Huntington's chorea described by Alzheimer (1911), assume real significance.

As had so often happened in relation to clinicophysiological correlation in cerebral disorders, the rush to stake out claims on the anatomical terra nova outran both the available physiological philosophy and the necessary neuropathological experience. Indeed the Croonian lectures of Kinnier Wilson (1925) are wholly devoted to a sobering criticism of the massive superstructure that had already burdened the topic. The difficulties that pervade the subject are derived from the very general nature of the pathological processes that affect these structures, the kaleidoscopic variations in resulting symptomatology, and the poorly understood part that the ganglia play in normal cerebral function.

Hepatolenticular Degeneration

The striking demonstration of lenticular cavitation in hepatolenticular degeneration (Wilson's disease), though important in other respects, was most misleading in its implication that the disease process was itself localised. The widespread nature of the gliosis that accompanies all forms of the disease (Hall 1921) is now generally recognised. That the disease is an inborn error of metabolism resulting in accumulations of protein-bound copper in many organs, particularly the liver and nervous system, is also well understood. Within the nervous system greatly increased concentrations of copper are present in the putamen and thalamus, and to a less extent in the cerebellum and cerebral cortex (Cumings 1948, Spillane et al. 1952, Cartwright et al. 1954). The striking improvement that can follow removal of small amounts of copper from the body by chelation indicates that, in some cases, a

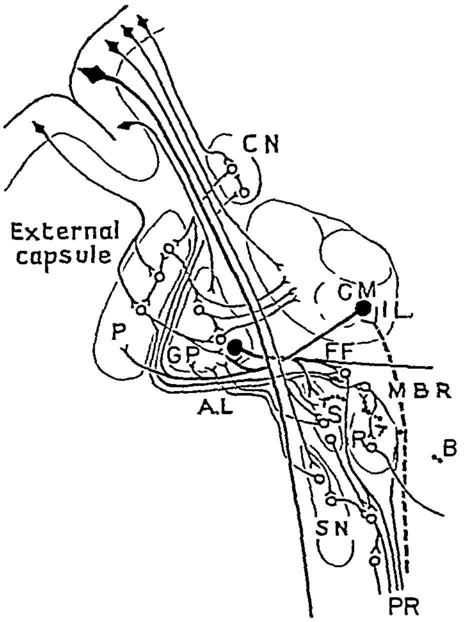

Fig. 1—Diagram of the chief connections of the basal ganglia.

The efferent systems of the globus pallidus (G P), putamen (P), and caudate nucleus (C.N) pass through the ansa lenticularis (A L) to the fields of Forel (F F). There they reach the subthalamic nucleus (S), the scattered nuclei of the midbrain reticulum (M B R.), substantia nigra (S N), and red nucleus (R.), with connections to the reticular nuclei of the pons (P R.). The reflex circuit has an afferent limb in the lemniscus and ascending tegmental tracts (represented as a broken line) through the intralaminar (I L) and central (C.M) nuclei of the thalamus. The midbrain and subthalamic reticular nuclei receive terminations of the brachium conjunctivum (dotted line B C.).

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* From the Croonian lectures for 1960, delivered before the Royal College of Physicians of London on Feb. 23 and 25.

relatively small fraction may in time interfere with vital enzyme function In the juvenile type such improvement is unfortunately offset by other unknown factors

When the symptoms start after the age of 20 the disorder appears as flapping tremors at the wrist and shoulders, which are absent at rest and provoked by movement The very diffuse gliosis of the nervous system that is then present makes it impossible to relate such incoordination to damage to any particular structure The tremor has some features in common with that caused by other types of damage to the midbrain reticulum The fate of such cases is usually determined by the severity of the associated hepatic cirrhosis If they survive for long a generalised mild muscular rigidity ultimately appears in all limbs, predominantly in flexion, in association with severe dysarthria and dementia There is then widespread fibrosis of the cortex, thalamus, and basal ganglia

In the juvenile types of Wilson's disease involuntary movements of a different kind occur These are at first small involuntary lapses in posture At or about the same time the natural facial expression changes, the mouth is *held more constantly open, and the eyelids blink seldom* The changes in expression, associated with slight postural changes in the hands in the nature of overextension of the fingers (fig *2a*), long precede the dysarthria and facile smile that were noted by Wilson Gradually the postures of the limbs become more stiff—at first in walking, when they tend to overextension first on one side and then on the other—leading to an awkward clumsy gait A plastic rigidity is then apparent in the affected limbs It is at this time that a slurred dysarthria is usually first noticed As the disorder progresses first one then the other arm becomes flexed in a hemiplegic posture, and the lower limbs become more constantly extended As these postures develop, tremor usually appears In some patients the tremor is that of the adult type of the disease, a rapid alternating flapping at the wrist and fingers In others it begins as athetosis, with slow swings from overextension of the hand to overflexion In this type the swing of movement may in time accelerate and make gradual transition into a parkinsonian type of tremor In most patients the swings of athetoid movement become slowed by increasing rigidity, the hand becomes more continually flexed and the ankles overextended as part of the terminal hemiplegic dystonia that was illustrated so well in Wilson's original description

I should like to draw particular attention to the evolution of the terminal dystonic state in hemiplegic attitude, for this has, in my experience, been invariably present when bilateral rarefaction or frank cavitation of the putamen has occurred In time there is yet a further change in the symptomatology, in the nature of lessening of the hemiplegic rigidity, and its conversion into a state of mild general flexion (fig *2b*), with flexed wrists and extended fingers and ankles If the patient is lifted from the bed, the limbs still stiffen, resuming in some degree the earlier rigid hemiplegic posture (fig *2c*) I shall later return to the significance of these postures, for they are a key to much that is obscure in the pathophysiology of the basal ganglia

Huntington's Chorea

It is not necessary here to outline the characteristics of Huntington's chorea except to point out some distinctive

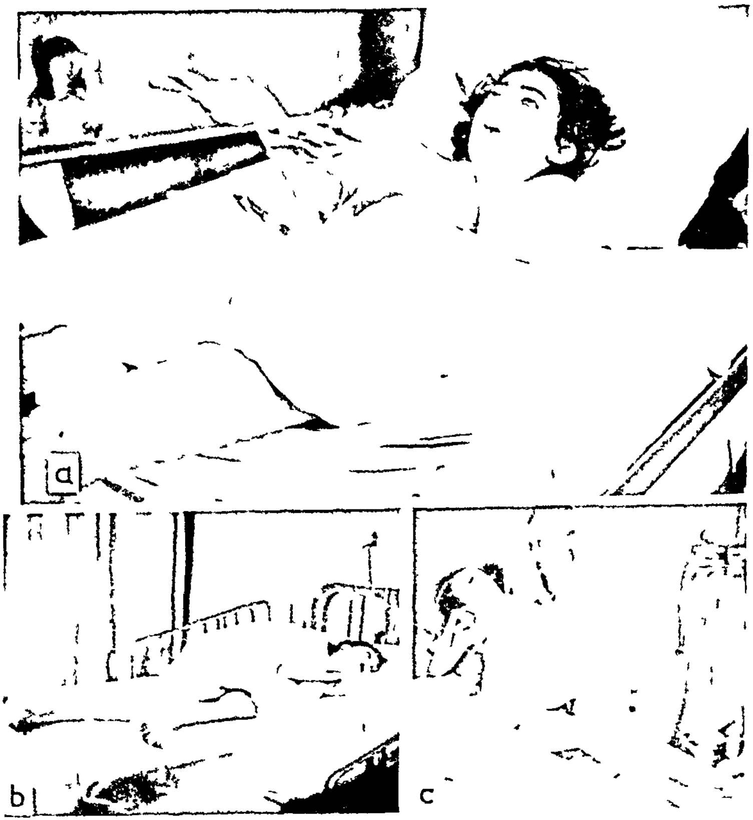

Fig 2—To show (*a*) the early abnormalities of posture in a patient of 16 beginning to show signs of hepatolenticular degeneration *In (b) is shown the posture of the* same patient 4 years later in an advanced stage of the disease (note the overflexed wrists with extended fingers) If the patient is lifted from contact with the surface of the bed (*c*) all limbs stiffen and the lower limbs extend

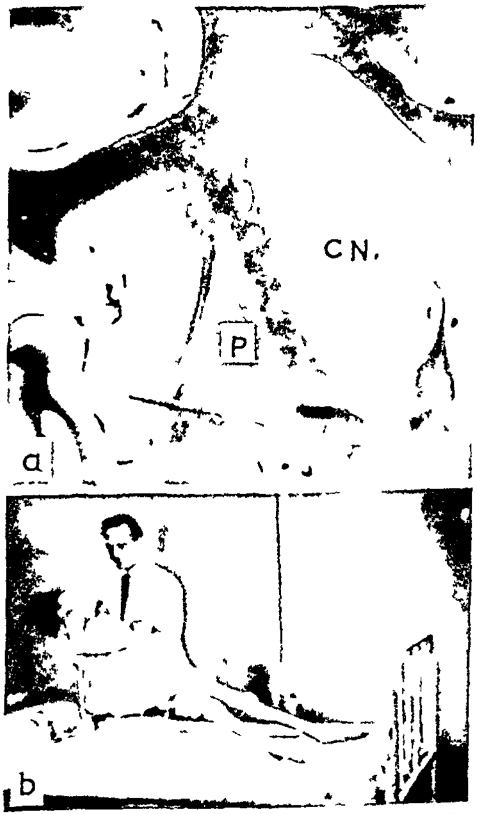

Fig 3—To show (*a*) the extreme atrophy of the caudate nucleus (C N) and to a less degree of the middle third of the putamen (P) in an advanced stage of Huntington's chorea; and (*b*) the rigid posture when such a choreic patient is raised from the bed

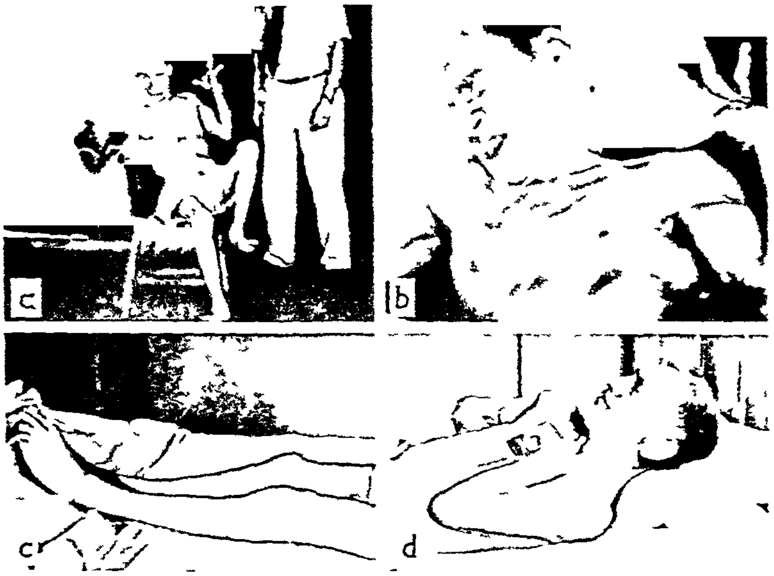

Fig 4—To show the "mobile spasm" with athetosis of hands and lips (*a* and *b*) in double athetosis. In the terminal stage a rigid posture of extension of the lower limbs (*c*) and flexion of the upper limbs (*d*) replaces the "mobile spasm"

features of the involuntary movements and postures The movements are essentially labile and haphazard in distribution. I have described elsewhere (Denny-Brown 1950) how the movements of the hands and arms gradually assume the swings of posture seen in athetosis, though at a faster rate. This is first seen in walking The movements of the lips and jaw gradually develop the wider amplitude, with associated incoordinate action of the platysma muscles, that is a feature of double athetosis For a long time the limbs are hypotonic, but the posture gradually becomes more stooped, and in late stages of the disease rigidity may appear, with more characteristic slower athetoid movements The posture is then a rigid hemiplegic attitude, which is greatly intensified by raising the patient from contact with any surface (fig 3) The arms are strongly flexed, and the legs and ankles stiffly extended. This posture is the same as that mentioned as a late stage of Wilson's disease

When the onset is early, rigidity may be the most prominent symptom (Kehrer 1928) There is then close resemblance to parkinsonism, including pill-rolling tremor of the fingers (Fleischhacker 1924, Josephy 1936) In a few patients unmistakable parkinsonism develops later in life (Chandler et al. 1960) though the lower limbs are, in my experience, more often extended stiffly than flexed in the usual parkinsonian posture. Besides atrophy of the frontal cortex shrinkage of the caudate nuclei is almost universally present, together with some loss of cells in the middle third of the putamen (Marie and Lhermitte 1914, Dunlap 1927) with pallor of the corticostriate and striopallidal systems (fig 3) A condition of fibrous scarring of the putamen, called "status fibrosus" by the Vogts (1920) and Jakob (1923), has been found in the cases presenting rigidity (Bielschowsky 1919, Terplan 1924 Freund 1925) In some cases the degeneration extends to the globus pallidus and subthalamic nuclei The extrapyramidal manifestations of Huntington's chorea, as with Wilson's disease, are seen to form a spectrum of types of movement disorder in relation to an evolving pathology, ranging from early myoclonic twitchings in some cases to torsion spasm and rigidity and, more rarely, parkinsonism The most characteristic choreic movements reflect only the usual early affection of caudate nucleus and frontal cortex.

Double Athetosis

The case selected by Vogt (1911) as the prototype of striatal disease presented an unusually well-localised marbled scar in the outer segment of the putamen on both sides The clinical symptoms are usually a bilateral labile type of athetosis affecting all parts, but particularly the hands, mouth, and neck, and present from the first year of life The condition is now well recognised, and is usually called "double athetosis" (fig 4*a* and *b*) The scar tissue appears to be a static inactive process Many follow Courville (1953) in attributing it to anoxia at birth. In several cases there has been similar scarring of the cerebral cortex (Alexander 1942), but there is no doubt that the lesion in the putamen can occur alone, and in association with a bilateral mobile type of athetosis present from soon after birth. In many cases rigidity of the limbs appears later, gradually slowing the athetosis to "mobile spasm" and leading ultimately to intense flexion of the upper limbs and extension of the lower limbs (fig 4*c* and *d*) When rigidity has complicated athetosis in this way the scarring of the putamen is usually more extensive, but few cases have been analysed from this point of view

Dystonia Musculorum Deformans

In its progressive form, dystonia is the most striking and grotesque of all neurological disorders The progressive small spasms of flexion of a lower limb, or alternatively of torticollis, that are usually the first manifestations in early childhood, first appear as additions to movements such as walking Only when continuous maintenance of the abnormal posture occurs is the dystonic condition recognised. Though I have earlier indicated the essentially athetoid character of the beginning of the disorder (Denny-Brown 1945), its relation to athetosis is still overlooked, for the first signs are spasms in willed movement rather than involuntary movements. As the disorder progresses new intermittent elements of athetoid spasm make their appearance, they are set up, like the first, by any stimulation or attempted movement. but they gradually become more constant. The cumulative steady spasm of flexion of proximal joints has added to it extension of the fingers and toes, retraction of the jaw and lordosis The later addition of intermittent spasm in antagonistic muscles followed by continued contraction in antagonists, leads to the great deformity Unless there is accompanying spasticity, the asymmetrical postures and movements can be profoundly changed by altering the areas of body in contact with the bed or examining table. If the patient is lifted free from all contact with the body surface, save for support under the axilla, the upper limbs flex and the lower limbs extend in hemiplegic posture (fig 5) If movements have been in progress they cease when the child is suspended When the patient lies on one side the lowermost limbs extend and the uppermost flex These changes indicate that reflex effects from contact between the body and supporting surface are important factors in the production of the abnormal movements and postures

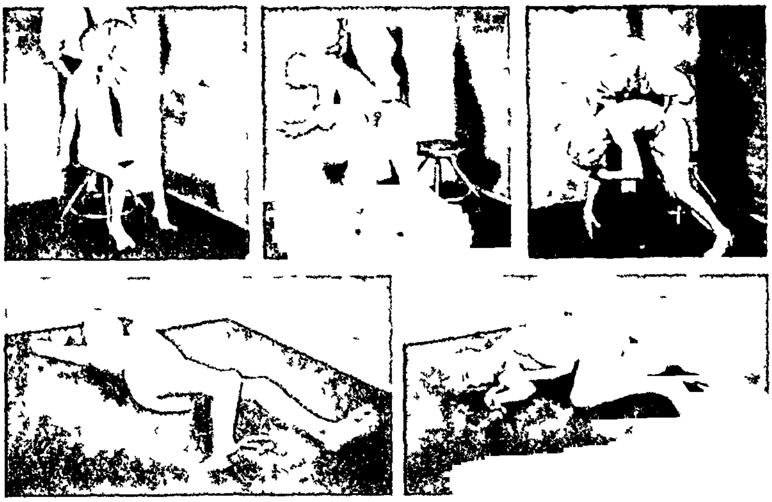

Fig 5—Dystonia musculorum deformans To show the abnormal attitudes and their modification by suspending the patient and by lying on a flat surface
(Photographed at Wrentham State School, with kind permission of Dr Carl Quinn)

Dystonia is a symptom complex that has many causes, but the irregular and grotesque progressive deformity described above, with cumulative development in one body part after another, has not been clearly correlated with pathological processes other than status marmoratus, which closely resembles the lesion of double athetosis, but usually involves the thalamus and cerebral cortex in addition to the putamen Thomalla (1918), Wimmer (1921), Jakob (1932), and others have reported the lesions of Wilson's disease in relation to relatively symmetrical dystonia Lethargic encephalitis was undoubtedly the cause of many cases of asymmetrical dystonia of partial and arrested types The cases of Cassirer (1929), Jakob (1923), Marinesco and Nicolesco (1929) and Laruelle and van Bogaert (1929) showed milder changes in the form of pallor of the globus pallidus and cell loss in the putamen There is some possibility that such cases are postencephalitic

More Diffuse Lesions of the Basal Ganglia

From the great variety of diffuse degenerative processes that affect the basal ganglia, I have singled out Wilson's disease, Huntington's chorea, and status marmoratus as examples where rigid " dystonic " states can be related to relatively localised destruction of the putamen Before turning to the problem of parkinsonism, we should briefly review some of the other types of diffuse pathology that affect the basal ganglia These are all rare and obscure syndromes, and I shall here only comment on the type of movement disorder in relation to anatomical lesion

Calcification of the basal ganglia (Fahr's syndrome) is an affection of the walls of small blood-vessels of these organs that may reach considerable intensity, even to the degree of visibility in skull X-rays (Fahr 1930), without neurological symptoms There may or may not be associated hypoparathyroidism (Sugar 1953) The neurological disorder that eventually appears is a generalised rigidity, most commonly beginning in the lower limbs (Fritsche 1935, Chavany et al 1949), with or without athetoid movements Parkinsonism developed in middle life in the patients of Jakob (1923) and of Alexander and Tucker (1949) The calcification in such cases begins on the border between the putamen and globus pallidus In a remarkable familial case of my colleague, Dr Paul Yakovlev, such calcification resulted in dysarthria with intense ridigity of all limbs in flexion

Similar flexion postures eventually result from diffuse *lipidosis* of the juvenile type (Sjogren 1931, Watson and Denny-Brown 1953) Similarly in the *Hallervorden-Spatz syndrome*, where deposits of iron-containing pigment accumulate in the globus pallidus, thalamus, substantia nigra, and dentate nuclei, there results a diffuse rigidity of the limbs in flexion, with or without athetosis It is also notable that, both in this syndrome and in lipidosis, there is a liability to sudden jerks of the limbs in flexion (myoclonus) as a prelude to the eventual postural change

The Enigma of Parkinsonism

The most common of extrapyramidal syndromes—parkinsonism—presents the most difficult problems in this whole group of diseases There is still no agreement as to the essential change in anatomical structure

The pallor of the ansa lenticularis and related efferent pathways of the pallidum, and the progressive loss of cells in the globus pallidus and, to a less extent, the striatum, described by Jelgersma (1908) and by Lewy (1913), have been found by many others (Lhermitte and Cornil 1921b, Bielschowsky 1922, Jakob 1923, Foix and Nicolesco 1925) In 1919 Tretiakoff drew attention to some loss of cells in the substantia nigra in paralysis agitans, as well as to the severe destruction of this nucleus in postencephalitic parkinsonism This feature of the disease has gained greater emphasis in the past twenty-five years (Hassler 1937a and b, Benda and Cobb 1942) Greenfield and Bosanquet (1953) have confirmed scattered cellular changes in the locus cœruleus of the pontine tegmentum, as well as in the substantia nigra, found earlier by Foix and Nicolesco, and by Hassler In his posthumous textbook on neuropathology, Greenfield (1958) states that the lesions in the globus pallidus, though constant and sometimes severe, are " essentially those of senility "

Our own pathological material in the Boston City Hospital consists of 21 cases, 5 of them are clearly postencephalitic, 7 have atherosclerotic lacunar lesions in the putamen, and 9 could be clearly calssified clinically and pathologically as idiopathic paralysis agitans Only 2 cases had been subjected to serial whole-brain sections, but multiple sections of the basal ganglia and midbrain of all the others were available for study

All cases of parkinsonism exhibited some degree of pallor of the globus pallidus and the ansa lenticularis, in sections stained for myelin sheaths The corresponding loss of nerve-fibres was more impressive than loss of nerve-cells In *paralysis agitans* the pallor was usually uneven, and foci of loss or thinning of myelin sheaths were particularly evident in the outer pallidum near the external lamina In Nissl sections such foci were represented by small inconspicuous areas of loss of cells from the otherwise evenly scattered pattern of pallidal cells In 2 cases small concretions were present in the ground substance, not directly related to the foci Gliosis was mild in degree In no case was there any evident disease of blood-vessels, other than some mild siderosis in 2 cases (a change commonly found in the globus pallidus after middle life) In one patient who died after a head injury all striopallidal and corticopallidal fibres stained very poorly compared with the pallidal efferents in the ansa lenticularis In the most severely affected cases all the pallidal cells were shrunken and stained poorly, and their lipid content appeared to be increased in relation to their size In 5 cases, and doubtfully in 2 the substantia nigra showed the small lesions described by Hassler No cell or fibre lesion was found in the nigra in 2 cases

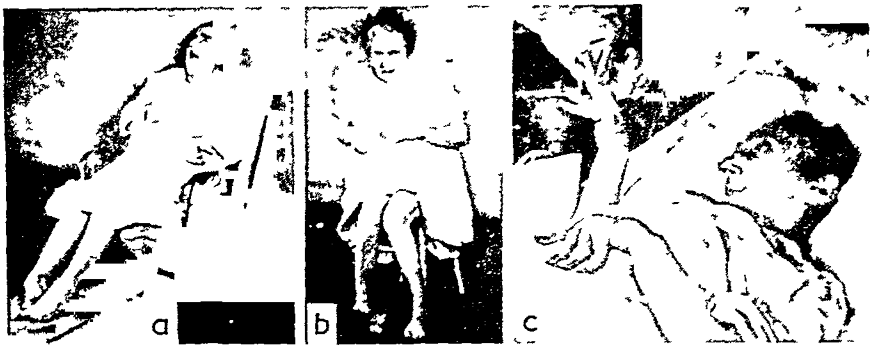

Fig 6—Terminal stages of paralysis agitans, to show flexion dystonia

The lesion of the globus pallidus is described by Bielschowsky (1922), and in detail by Foix and Nicolesco (1923, 1925), who called it "paravascular degeneration." It was regarded as the first stage of a change that later leads to more evident loss of tissue elements (*etat precrible*), and later still to pericapillary destruction of tissue (*etat criblé*). It should be emphasised, however, that in paralysis agitans with paravascular degeneration no evidence of change in the walls of blood-vessels can usually be found. If siderosis is present it must be an independent abnormality, for it can be severe in degree without producing paravascular degeneration. The pattern of tissue damage reflects some peculiarity in the permeability of the smallest blood-vessels in this area, and is common in the earliest stage of some of the metabolic diseases affecting the basal ganglia.

When *atherosclerosis* has affected the vessels of the basal ganglia, lesions of the putamen are more obvious than those of the globus pallidus. Lacunes of softening appear in the putamen surrounded by foci of *etat crible*. The clinical state is then most commonly that of pseudobulbar paralysis, with or without damage to the internal capsule and cerebral white matter. In 2 of our cases with typical parkinsonian tremor and attitude, mild *crible* lesions were limited to the internal part of the putamen and outer globus pallidus. Only associated atherosclerosis of the arterioles, and the presence of the *crible* state in the putamen, then differentiate arteriosclerotic parkinsonism of this type from what we would call true paralysis agitans. The pericapillary degeneration itself is more severe but otherwise closely resembles "paravascular degeneration." There may be small foci of similar paravascular degeneration in the substantia nigra, but these are not necessarily present. Paravascular degeneration, I believe, is not directly the result of atherosclerosis but is worsened in extent and degree by its presence. The evidence for this will presented elsewhere. The occasional cell inclusions that have been noted by Lewy (1923), Hassler (1937a), and Greenfield and Bosanquet (1953) in the substantia nigra have been found in the Boston City Hospital in all types of case. I am not convinced that they are a primary or specific change.

In my monograph in 1945 I made a sharp distinction between true paralysis agitans and arteriosclerotic parkinsonism. With greater experience I have to admit that this distinction is not absolute. There is every degree of transition. At one end of the scale one can recognise a slowly progressive gentle tremor at rest, with mild rigidity, that may begin in the fifth decade, with slight paravascular changes limited to the globus pallidus. At the other extreme the marked rigidity and fixed hemiplegic posture of the pseudobulbar type is related to the "lacunar" state, with multiple small infarcts of the putamen. Between lies every conceivable relative proportion of tremor and rigidity. Thus arteriosclerotic parkinsonism may begin with rigidity, tonic grasp, and tonic foot response, with very little tremor. In this type the putamen appears to be invariably damaged, and is perhaps first affected. Yet rigidity can also occur with pallidal lesions. A patient of mine, an 81-year-old man who had first developed typical parkinsonian rigidity and tremor twenty-one days before death, presented recent partial infarction (circumscribed pallor) of the globus pallidus on both sides. There was no change in the substantia nigra. Lhermitte and Cornil (1921a) cited a similar case.

The symptomatology of paralysis agitans consists of the well-known tremor and rigidity. In the tremor the opposed thumb beats against the first finger, and is associated with tremor of the lips and tongue before other parts. The soft yielding plastic rigidity of paralysis agitans appears first in the flexors of the upper limbs, and is associated with delay in initiation of movement, though the relative degrees of bradykinesia and objective rigidity are greatly variable. Seldom is it emphasised that in typical paralysis agitans the rigidity is invariably associated with change in posture, its preponderance in the flexor groups gradually leading to the stooped posture with flexed limbs, fixed facies with staring eyes, and open mouth, by which parkinsonism can be recognised in a photograph. It is important also to emphasise that in the natural course of the disease the postural change gradually worsens until in a terminal stage all the limbs are drawn into a fixed attitude of general flexion (fig 6). The wrists are then strongly flexed and pronated, the fingers are extended, and the ankles are plantar flexed. Attempted displacement of any part away from this attitude then meets a mounting resistance, and the part rapidly returns to its resting attitude. This terminal loss of plasticity is associated with great lessening or loss of the tremor. Speech is also lost or reduced to a mumble.

Studies of arteriosclerotic parkinsonism indicate that the coarser the lesions of the external segment of the globus pallidus the more rapid has been the development of dystonia, with correspondingly less evident tremor. If the putamen is involved tremor may not occur, and the rigidity is then not only more intense but also involves the extensors of the lower limbs and the flexors of the upper limbs (hemiplegic distribution). The pattern of rigidity as well as its intensity reflect the more lateral and lacunar lesions.

In *postencephalitic parkinsonism*, though the same tremor may be present, it is more often damped or abolished by an intense asymmetrical rigidity. The rigidity passes more rapidly into the fixed attitudes of dystonia, leading to torticollis, scoliosis, and grotesque postures of the limbs. On the side on which dystonia was absent or delayed in appearance, the tremor tends to be more violent and more extensive than in paralysis agitans. In addition various forced movements and compulsions, of which the oculogyric crises are the best known, are peculiar to the postencephalitic state. Like others, we at Boston have found a severe destruction of the substantia nigra in all cases, but we have also found a diffuse pallor of the fibre systems of the globus pallidus Obvious nerve-cell changes in the globus pallidus or striatum are seldom found, but small foci of lesser change are common More important, we have often found loss of the small thinly medullated fibres entering the external putamen from the external capsule, and the external lamina of the globus pallidus from the internal capsule, with or without paucity of striopallidal fibres There is corresponding gliosis This inconspicuous change is of great significance in relation to the prominence of symptoms of corticostriate and corticopallidal disorder, and I shall return to it in my second lecture In the acute stages of lethargic encephalitis destruction of the substantia nigra was commonly found in patients without parkinsonism (Meyer 1923, Holzer 1926) If 75% of the substantia nigra is destroyed in most cases of postencephalitic parkinsonism, this still fails to account for the varied and complex disorders of motor function of that disease, and their delay in appearance Still less is the similar symptomatology in paralysis agitans explained by the inconstant meagre changes in the substantia nigra and locus cœruleus in that disease

Focal Lesions of the Basal Ganglia

The natural history of diseases that commonly affect the basal ganglia of the brain has been outlined in order to draw attention to their general tendency to produce involuntary movements that progress slowly to states of rigid maintenance of abnormal attitude We shall now turn to the effects of acute destructive lesions, which, by contrast, produce striking disorders of attitude from their beginning

Necrosis of the Striatum (Putamen and Caudate Nuclei)

Bilateral symmetrical necrosis of the caudate nucleus and putamen has been found in conditions such as death from status epilepticus in children, when anoxic damage to small vessels is presumably the primary mechanism

Marinesco and Draganesco (1929) describe this condition after convulsions in a child aged $4^1/_2$ years, who survived to the age of 6 There was patchy laminar necrosis of the cerebral cortex, and only mild degenerative changes were found in the globus pallidus Until death the child lay in an unresponsive state without making purposeful movements There was complete absence of speech, and swallowing was difficult At first the limbs were extremely rigid in flexion, but they would extend with changes in posture, and athetoid movements were present Later rigidity was less evident when the child lay on a surface, though all the limbs were semiflexed, the wrists pronated, the fingers flexed, the ankles extended, and the toes plantar flexed When the child was suspended in air, all the limbs became intensely rigid, the arms flexed, the hands clenched, the lower limbs extended, the ankles inverted, and the toes flexed This posture would persist as long as the child was suspended This phenomenon of the appearance of rigidity when the patient is lifted from a surface is commonly called ‘ the Foerster syndrome ” Foerster (1909), however, described only the atonic type of cerebrocerebellar diplegia, and the extension of the limbs when suspended appears to have been first described by Batten and von Wyss (1915)

Hawke and Donohue (1951) described, in a 13-year-old child, a similar complete bilateral necrosis of the whole corpus striatum, caudate, putamen, and globus pallidus, which occurred during a febrile illness complicating otitis media, without any known episode of anoxia During two months of survival the child did not speak or respond to commands The eyes would follow the movements of another person, and even moving objects late in the survival period The muscles were at first hypotonic, but they gradually became stiff in flexion, particularly during passive movement Occasional myoclonic twitching of muscles was observed The remarkable phenomenon of rigidity when suspended is not mentioned by these workers Similar cases have been reported by Verhaart (1938)

Complete clinical and anatomical studies of cases of unilateral destruction of the putamen and caudate nucleus are equally rare I cannot here discuss in detail such a case in the collection of my colleague Dr Yakovlev, suffice it to say that for the last ten years, before death at the age of 25, the patient had presented a dystonic contracture of the right arm in flexion and the right leg in extension, with consistent flexor plantar responses There was a severe spastic dysarthria Mobile athetoid spasm of the hand had preceded the dystonic attitude of extended fingers, and flexed wrist and elbow Steck (1921) reported a similar case, though the dystonia was not fully described

When bilateral partial cystic infarction of the putamen has occurred without damage to the internal capsule, the clinical condition has been that of pseudobulbar palsy (as first described by Richard Bright 1831) The pseudobulbar state resulting from Wilson's disease, and the condition resulting from manganese poisoning (Peñalver 1955, Berry and Bidwai 1959), have obvious features in common

Necrosis of the Globus Pallidus

One of the most striking lesions of the basal ganglia is the symmetrical necrosis of the globus pallidus found in patients who have had an episode of coma as a result of inhalation of coal gas, or carbon monoxide, or occasionally nitrous oxide, and rarely in those who have had other types of asphyxic anoxia It can also follow intoxication by carbon disulphide (Richter 1945)

The patient commonly recovers from the initial coma, and he may be discharged from hospital apparently completely relieved, or with only slight mental confusion After one to three weeks, he may then relapse into coma a second time, and succumb in that state Most often the delayed relapse presents as the onset of an akinetic mute state, with rigidity In other cases the relapse takes the form of renewed confusion in which elements of visual agnosia and catatonic postures are prominent, presumably resulting from lesions of cerebral white matter In a few cases a mild parkinsonian rigidity makes its appearance within six weeks of recovery from the initial coma

I need not here discuss the many interesting aspects of the neuropathology, which has recently been reviewed by Meyer (1958), whose earlier papers are among the most authoritative Widespread patchy areas of cortical ischæmic damage may occur Their presence is to be suspected whenever mental confusion is persistent The lesion that concerns us here more particularly is necrosis of the globus pallidus It is commonly found when death has occurred soon after exposure, without recovery from coma, and it is usually bilateral and approximately symmetrical Some part of the globus pallidus, usually the most anterior part of the internal segment, is the site of a hæmorrhagic softening, commonly occupying only a small part (10 to 20%) of the nucleus There is usually no incrustation of the vessels in this early stage The necrosis is clearly secondary to vascular damage

Where death has occurred after a delayed relapse, with onset of akinesia and rigidity, the infarct is usually larger, and it may involve the external segment or even portions of the putamen An associated lesion of the substantia nigra has been reported (Hiller 1924) but is very rarely found In a few such cases evidence of cortical damage is very slight, and white-matter lesions have been absent

Of 2 such cases followed closely in life, 1 showed an unvarying akinetic state for six months

This 58-year-old man was found in coma in a small unven-

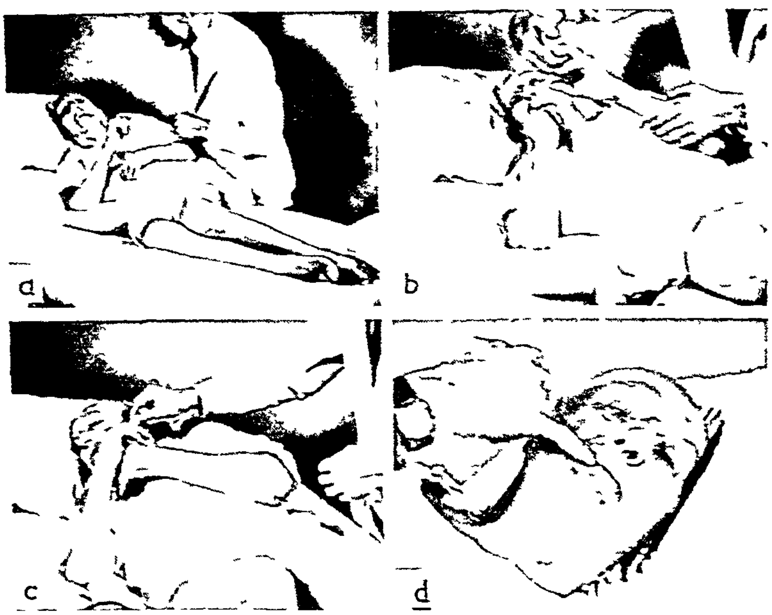

Fig 7—Carbon-monoxide poisoning: (a) to show the flexed akinetic mute state, (b) the absence of grasp response, (c) the small response to pinprick on the face, and (d) tight closure of the mouth when lips were touched.

tilated hut, with a burnt-out brazier fire, without chimney. He lay unreflexic for a day but then made a rapid recovery. Eight days later he was able to speak, to read a newspaper, and to travel from Florida to Boston. On the ninth day he was found to be very drowsy, and he rapidly lapsed into an unresponsive state, with arms and legs moderately rigid in semiflexion. His eyes were open and they occasionally followed the movements of the examiner. He slowly scratched the face if pricked with a pin, but he gave no other reaction. The deep-tendon reflexes were present but not increased. Both plantar responses were extensor. The face was expressionless. Swallowing was possible only if fluid was introduced far back into the mouth. Any attempt to open the lips or mouth passively met increasing resistance. The limbs were held continuously in a semiflexed posture, the wrists were flexed, and the ankles extended. Because of mild plastic rigidity, they resisted attempts to extend them passively. The fingers were extended and were not used, except for a feeble brushing movement at a noxious stimulus to the face. There was no grasp response to a light stimulus, but, occasionally, after heavy stroking, a feeble grasp was obtained. Such responses are illustrated in fig 7 from another patient who survived in an identical state for many months but in whom necropsy was not obtained.

In the first patient examination of the brain showed the characteristic lesions of the globus pallidus. There was no lesion of the substantia nigra, or thalamus, or other part of the extrapyramidal system. The cortex was virtually unaffected, but some patchy lesions in the frontal white matter of the orbital cortex were found on both sides, with a smaller lesion in the deep parietotemporal white matter. In this case vascular lesions of two different stages were apparent, supporting the hypothesis that the lesion had in fact enlarged after the latent interval. The occluded vessels were calcified in the area of more recent extension of softening.

In general small pallidal lesions have not been associated with extrapyramidal signs other than slowness in initiation of movement. The most intense akinesia and rigidity has followed large lesions. Where rigidity in flexion has followed after a long interval, I suspect that the lesion has enlarged because of delayed vascular changes, even after as long as seven years (Alexander 1942), and even forty-nine years in the report of Yakovlev (1944).

Focal Subthalamic Lesions

Discussion of the involuntary movements of *hemiballismus* resulting from lesions in the subthalamic nucleus will have to be omitted, except to emphasise that the characteristic movement involves a rotary element at proximal joints. This rotary element also appears in the posthemiplegic chorea associated with some types of thalamic lesion, and in the “ midbrain ” tremor so well described by Holmes (1904). When progressive lesions affect the general region of the midbrain tegmentum, rigid extension and internal rotation of all limbs eventually appears. This is the most common type of “ decerebrate rigidity ” encountered in man. Cathala (1922) has described a unilateral example resulting from tumour of the tectal region.

General Conclusions

In this necessarily abbreviated account of the general aspects of the symptomatology of diseases of the basal ganglia I have emphasised the diffuse nature of the pathology of such diseases, and their general tendency to produce involuntary movements that gradually make transition to abnormal postures. These two features are of special importance, for one of the most baffling aspects of these syndromes has been the inability of the physiologist to reproduce them by surgical or electrolytic lesions. It has not been appreciated that focal necrotic lesions of the putamen and globus pallidus can in man produce the terminal states that are seldom reached by degenerative diseases of the same structures. In particular I would stress the akinetic mute state of general flexion of all limbs, with pronated wrists and extended fingers, that is characteristic of severe destruction of the globus pallidus (“ pallidal syndrome ”). In milder degrees there is associated tremor of parkinsonian type. In contrast the more rigid flexion of upper limbs and extension of the lower limbs, greatly intensified by suspending the patient free of contact with body surface, is characteristic of destruction of the putamen and caudate nucleus (“ striatal syndrome ”). Lesser degrees of this disorder are characterised by athetosis and “ mobile spasm ”. With these two basic postural changes in mind their physiological meaning, and the significance of the disorders of movement that are associated with them, may be approached.

(The references will appear at the end of the second lecture.)

“ The more efficient society becomes at rapidly modifying our environment and our ways of life the more unpredictable are the responses of man to the new conditions of his own making. In order to meet its professional responsibilities, medicine must add to its preoccupation with disease the study of the responses of normal man to the rapidly changing environment. It must supplement the knowledge of pathology with a new science which might be called biological technology. At least, this is the conviction which has led me, a bacteriologist, to focus my thoughts increasingly on the factors, external and internal, which condition the response of man to the microbes which are an ubiquitous part of his environment.”
—René J. Dubos. *J. Amer. med. Ass.* 1960, 174, 505

HYPERSENSITIVITY TO MILK AND SUDDEN DEATH IN INFANCY

W E Parish[*]
B A Cantab , B V Sc Lpool

A M Barrett
M D Cantab

OF THE DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAMBRIDGE

R R A Coombs
Ph D Cantab , M R C V S Edin
DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAMBRIDGE

Mavis Gunther
M D Cantab
RESEARCH WORKER, OBSTETRIC DEPARTMENT,
UNIVERSITY COLLEGE HOSPITAL, LONDON, W C 1

Francis E Camps
M D Lond , D T M & H
READER IN FORENSIC MEDICINE, DEPARTMENT OF FORENSIC MEDICINE,
LONDON HOSPITAL MEDICAL COLLEGE, E 1

In a review of the possible causes of sudden death in infancy, Barrett (1954) suggested that of such cases " perhaps the majority are due to the inhalation of regurgitated food into the lungs " The inhaled food might not cause death by directly obstructing the air-passages an amount of milk too small to cause immediate asphyxia might excite an inflammatory reaction accompanied by pulmonary œdema, or the absorption of undue amounts of milk derivatives into the blood-stream might cause a state of shock

Such effects of inhaled food or vomit, if they occur, might be due either to an inherent toxicity of the inhaled material when it enters the body by this abnormal route, or to an anaphylactic type of reaction resulting from antigenic sensitisation

We present some experimental evidence which suggests that the second, but not the first, of these two mechanisms is indeed a possible cause of sudden death in infancy The hypothesis is that some infants may be in a hypersensitive state from the development of antibodies to the proteins of milk absorbed from the alimentary tract Infants often regurgitate stomach contents while asleep, and should some of this material be aspirated into the respiratory tract of an infant which has become hypersensitive, the result might be fatal

There is no doubt that most infants fed on cow's milk develop antibodies to the proteins of the milk Gunther, Aschaffenburg, Matthews, Parish, and Coombs (1960) using a sensitive technique—the coated tanned red-cell test of Boyden (1951)—showed milk antibodies in normal children aged 7–97 weeks in a titre up to 1000 with a modal distribution around a titre of 64

There thus seems to be ample evidence that the majority of infants are immunised to some degree or other to the proteins of cow's milk, and the possibility exists that these or other types of antibody may sensitise the tissues of the infants Anderson and Schloss (1923) showed that in infants with some types of nutritional disorders, milk proteins were absorbed via the alimentary tract and that subsequently precipitins to milk protein could be shown in the infants' sera, and these antibodies could sensitise guineapigs passively to anaphylaxis According to Clein (1958), up to 6% of infants during the first few months of their lives are allergic to cow's milk

Parish, Barrett, and Coombs (1960) showed that administration of milk over the glottis into the larynx of unsensitised conscious guineapigs was for all intents and purposes without clinical effect On the other hand, a small amount of milk dropped into the larynx of sensitised guineapigs resulted in a characteristic anaphylactic reaction often leading to death The reaction itself and the pathological findings in such animals were those of frank anaphylaxis and did not resemble those seen in human cot-death cases If, however, the guineapigs were lightly anæsthetised—an experimental condition used to simulate the condition of the sleeping child—milk introduced into the larynx had quite a different effect In the unsensitised guineapigs there was no untoward effect, and even in the sensitised animals there was a complete absence of the usual features of anaphylaxis seen in a conscious animal Very soon after introducing the milk preparations into the larynx of an anæsthetised sensitised guineapig, the animal stopped breathing without any signs of struggle Death sometimes occurred immediately, but the majority of animals took deep breaths at 10–30-second intervals for a variable period Death was preceded by a short period of more rapid breathing, each respiratory effort being shallower than the preceding one, until, with a final nose-twitching, the animal died Others lingered for 20–60 minutes before death took place, or normal respiration was gradually resumed This sequence of events became recognised as characteristic, and was reproducible on challenge of all the anæsthetised sensitised animals The pathological findings in the animals which died resembled those in human cot-death cases

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The guineapigs each received one intraperitoneal injection

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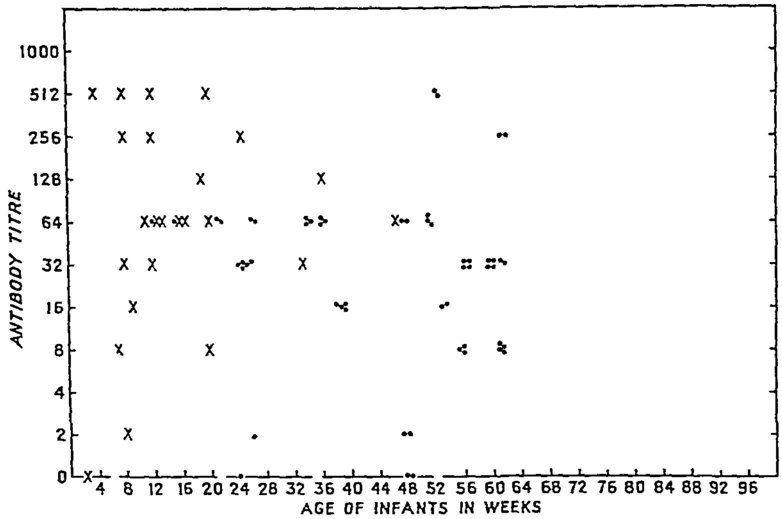

Fig 1—Titres of serum-antibody to cow's milk proteins at various ages in 24 'cot-death' cases (X) and in 286 normal infants (●)

A strict comparison of the two categories is not possible for the reasons stated in the test

of 1 ml reconstituted milk powder 2% w/v The inoculum consisted of the soluble and insoluble material

In experiments with human stomach-contents the animals were challenged on the 18th day after injection In experiments with milk proteins they were challenged on the 69th day

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Experimental Study

Serum Antibody Levels

Using coated tanned red cells Gunther et al (1960) tested the sera of 286 normal children aged 7–97 weeks (fig 1) Nearly all the sera contained measurable antibody to cow's milk proteins In distribution the mode fell around a titre of 64 Approximately 4% had a titre of 256, 1% a titre of 512, and one serum had a titre of 1000 The plot of serum titre against the age in weeks of the child is shown in fig 1

We have now tested sera from 24 cases of cot death for the titre of antibodies to cow's milk Only those cases of sudden death were included which, on the pathologist's report, could be considered as "cot-death" cases These infants were known to have been bottle-fed at the time of death, and milk was found in their stomachs at post mortem

The serum titres of antibody to cow's milk in the cot-death cases are also shown in fig 1 where the distribution can be seen in relation to that found in normal infants

The number of cases available so far is not sufficient for a final assessment, nor is the mode of selection in the two categories appropriate for a strict comparison between the serum levels in normal infants and in the cot-death cases In the first place approximately 32% of the normal infants were known to be mainly breast-fed at 6 weeks of age, while the cot-death cases studied were all bottle-fed at the time of death Moreover, the blood from normal infants was collected under ideal conditions and the sera frozen to −15°C within 5 hours of bleeding, while the blood from cot-death cases was obtained post mortem and often had considerable precipitates which had to be centrifuged out before testing However the high titres found in the sera of the majority of cot-death cases are in keeping with the possibility that, had these infants aspirated milk into their respiratory tracts, a lethal hypersensitivity reaction, as seen experimentally in guineapigs, might have occurred

We are not suggesting that the level of serum antibody is necessarily a measure of the degree of sensitivity, although for the type of anaphylactic reaction envisaged this cannot be excluded It does indicate, however, that the infants have received a considerable antigenic stimulation with cow's milk and are, for this reason, potentially sensitised to these proteins

Effect of Stomach Contents on Sensitised Guineapigs

In our previous experiments (Parish et al 1960) National dried milk was used as the material for challenge In the present paper we report a similar experiment but the material used was stomach contents from actual cot-death cases in which the infant's last feed had been from the bottle This was used because, in the hypothesis we put forward, we believe regurgitated stomach contents are the source of the aspirated material initiating the lethal reaction

In this experiment both sensitised and unsensitised (control) guineapigs were lightly anæsthetised with an intraperitoneal injection of pentobarbitone Approximately 15 minutes later, when the desired state of anæsthesia had been reached, 0 25 ml of a 1/2 dilution of stomach contents (0 125 ml of the original contents) was introduced into the larynx Stomach contents from 4 cases of cot death were used The tenaciousness of this material necessitated its dilution with an equal volume of saline to avoid mechanical obstruction of the respiratory tract of the guineapig, which is, of course, much narrower than that of the human infant The stomach contents were obtained from dead infants aged 2, 4, 8, and 22 weeks The larger lumps found in the stomach of the oldest child were first broken down in a Griffith grinder

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D aged 22 weeks	0 25 ml	D D D D − −	4/5	+ + − ± −	0/5

Scale of severity of clinical effects
D = death
+++ = severe respiratory embarrassment just insufficient to be fatal
++ = definite clinical disturbance but not severe
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HYPERSENSITIVITY TO MILK AND SUDDEN DEATH IN INFANCY

W E Parish * B A Cantab , B V Sc Lpool
A M Barrett M D Cantab
OF THE DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAMBRIDGE

R R A Coombs
Ph D Cantab , M R C V S Edin
DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAMBRIDGE

Mavis Gunther
M D Cantab
RESEARCH WORKER, OBSTETRIC DEPARTMENT,
UNIVERSITY COLLEGE HOSPITAL, LONDON, W C 1

Francis E Camps
M D Lond , D T M & H
READER IN FORENSIC MEDICINE, DEPARTMENT OF FORENSIC MEDICINE,
LONDON HOSPITAL MEDICAL COLLEGE, E 1

In a review of the possible causes of sudden death in infancy, Barrett (1954) suggested that of such cases " perhaps the majority are due to the inhalation of regurgitated food into the lungs " The inhaled food might not cause death by directly obstructing the air-passages an amount of milk too small to cause immediate asphyxia might excite an inflammatory reaction accompanied by pulmonary œdema, or the absorption of undue amounts of milk derivatives into the blood-stream might cause a state of shock

Such effects of inhaled food or vomit, if they occur, might be due either to an inherent toxicity of the inhaled material when it enters the body by this abnormal route, or to an anaphylactic type of reaction resulting from antigenic sensitisation

We present some experimental evidence which suggests that the second, but not the first, of these two mechanisms is indeed a possible cause of sudden death in infancy The hypothesis is that some infants may be in a hypersensitive state from the development of antibodies to the proteins of milk absorbed from the alimentary tract Infants often regurgitate stomach contents while asleep, and should some of this material be aspirated into the respiratory tract of an infant which has become hypersensitive, the result might be fatal

There is no doubt that most infants fed on cow's milk develop antibodies to the proteins of the milk Gunther, Aschaffenburg, Matthews, Parish, and Coombs (1960) using a sensitive technique—the coated tanned red-cell test of Boyden (1951)—showed milk antibodies in normal children aged 7–97 weeks in a titre up to 1000 with a modal distribution around a titre of 64

There thus seems to be ample evidence that the majority of *infants* are *immunised* to some degree or other to the proteins of cow's milk, and the possibility exists that these or other types of antibody may sensitise the tissues of the infants Anderson and Schloss (1923) showed that in infants with some types of nutritional disorders, milk proteins were absorbed via the alimentary tract and that subsequently precipitins to milk protein could be shown in the infants' sera, and these antibodies could sensitise guineapigs passively to anaphylaxis According to Clein (1958), up to 6% of infants during the first few months of their lives are allergic to cow's milk

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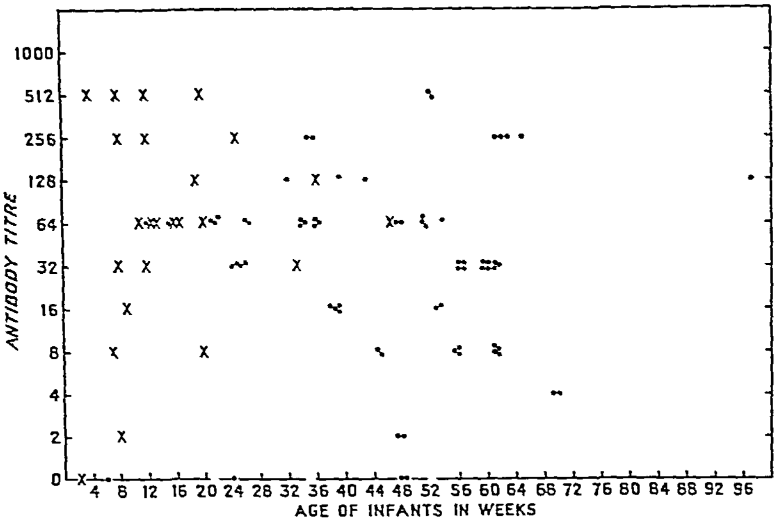

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Scale of severity of clinical effects

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——— =severe respiratory embarrassment just insufficient to be fatal

—— =definite clinical disturbance but not severe.

— =one or two signs of respiratory embarrassment but always mild.

— =no response

In the unsensitised guineapigs no deaths, and in the great majority of cases no effects, were observed On the other hand most of the sensitised animals exhibited the syndrome already described and died silently, without any struggle, and in a very short time Three animals recovered after a protracted period during which there were long spells of apnœa interrupted only by occasional weak gasps One of the sensitised animals was apparently unaffected The results are summarised in table I

Effect of Milk Proteins on Sensitised Guineapigs

In our earlier report (Parish et al 1960) we recorded the level of milk antibodies and the clinical sensitivity to challenge with milk at 17, 38, 64, and 92 days after a single sensitising injection Although in some animals the level of serum-antibody appeared to fall with the passage of time the animals were as sensitive clinically to the aspiration of milk on the 92nd day as they were earlier We wished to see if a similar lethal reaction could be produced by the individual component proteins of cow's milk

The guineapigs were sensitised as before by injecting intraperitoneally 2% w/v reconstituted National dried milk in a dose of 1 ml On the 69th day they were challenged via the respiratory tract while under light anæsthesia with 0 25 ml of (*a*) the soluble proteins in 10% w/v reconstituted milk powder (approximately 1% soluble proteins), (*b*) 1% casein, (*c*) 1% α-lactalbumin, or (*d*) 1% β-lactoglobulin The day before challenge each animal was bled and the serum subsequently tested for antibodies to reconstituted dried milk, and to the component protein with which the guineapig was challenged

The results of the serological tests, and the clinical effects on challenge are recorded in table II Casein, as might be expected, proved to be as effective as whole milk in producing lethal reactions In one of the previous papers (Gunther et al 1960) similarly sensitised guineapigs tested 17 days after injection had antibodies to α-lactalbumin but none to β-lactoglobulin In the present experiment no antibodies could be shown to α-lactalbumin 69 days after injection Clinically only very mild reactions were produced on challenging with α-lactalbumin, but with β-lactoglobulin the reactions were as severe as with casein or whole milk

TABLE II—LEVEL OF SERUM ANTIBODY TO MILK PROTEINS ON 69TH DAY AFTER INJECTION AND CHALLENGE OF SENSITISED GUINEAPIGS WITH COMPONENT PROTEINS OF COW'S MILK

Guinea pig	Challenged with	Serum antibody titre to				Clinical effect on challenge‡
		Reconst National dried milk	Casein	α lact albumin	β lacto-globulin	
1	Soluble material in reconstituted National dried milk*	16				+ +
2		16				D
3		32				+ + +
4		16				D
5						D
6	Casein†	8	16			D
7		16	16			+ +
8		128	64			D
9		16	16			D
10		16	16			D
11	α lactalbumin†	8		0		+
12		32		0		+
13		32		0		+
14		8		0		±
15		16		0		–
16	β lactoglobulin†	16			0	D
17		8			0	+ +
18		4			0	D
19		64			32	D
20		64			4	D

0 indicates a titre < 2

‡ Scale of severity of clinical effects—see table I

* Made up 10% w/v—approximately 1% soluble protein

† A 1% solution

Of thirty unsensitised (control) anæsthetised guineapigs challenged with soluble or insoluble milk preparations (Parish et al 1960) no reaction was observed in twenty-six—one showed a very mild reaction and two a moderate reaction One animal died but on subsequent investigation its serum was shown to contain what appeared to be a naturally occurring antibody to cow's milk proteins to a titre of 16

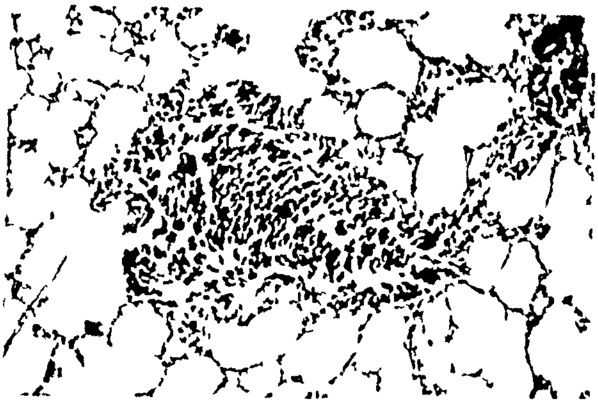

Fig 2—A bronchiole of anæsthetised sensitised guineapig which died soon after the introduction into its trachea of 0 25 ml of diluted (50%) stomach contents from a case of cot death (Hæmatoxylin and eosin ×120)

The bronchiole is so full of desquamated epithelial cells that in the photograph it is scarcely recognisable

We have thus shown that lethal reactions can be produced with casein and β-lactoglobulin On the other hand only mild reactions were obtained with α-lactalbumin However, further guineapigs will have to be tested at different periods after sensitisation before this protein can be considered less noxious than the other two

Pathological Findings in Sensitised Guineapigs

The histopathology of the lungs of sensitised guineapigs which died after inhalation, when anæsthetised, of total reconstituted dried milk, or its soluble or insoluble fractions, has already been described (Parish et al 1960) All the changes observed in the lungs of similarly sensitised guineapigs which died after the inhalation of casein or β-lactoglobulin closely resembled those in the earlier experiments *In those sensitised animals challenged with β-lactoglobulin or casein, the chief* features were generalised congestion with occasional areas of partial collapse, and serous exudate or œdematous transudate Cellular infiltration in the œdematous areas, or in the peribronchial, or periarteriolar connective tissue consisted chiefly of mononuclear cells Many of these were macrophages with variable numbers of lymphocytes and, in some animals, plasma-cells, but there were few polymorphonuclear cells A common finding was the desquamation of large numbers of single, intact, apparently normal, epithelial cells of the bronchial wall into the lumen of the small bronchioles

The histopathological changes in the lungs of sensitised anæsthetised guineapigs which had died as a result of inhaling small amounts of the stomach contents obtained from cot-death cases were similar to those observed in sensitised animals inhaling milk Generalised congestion was usual, but there was only an occasional small area of œdema and little cellular infiltration The infiltrating cells were chiefly macrophages, though there was an increased number of polymorphonuclear leucocytes—more than observed in animals challenged by milk The majority of the leucocytes were eosinophils, and in some preparations they were found also in the peribronchial connective tissue There was some evidence that the bronchioles and arterioles had undergone contraction, but further study of this feature is required Many of the medium-sized and smaller bronchioles contained large numbers of desquamated cells, sometimes these completely filled the lumen (fig 2) Bronchioles thus affected could be found in all the lung material, but the number varied from animal to animal The trachea was usually congested and in some cases infiltrated by eosinophils, the epithelium of the trachea was not desquamated

The unsensitised—i e, normal anæsthetised control guineapigs which had inhaled the stomach contents obtained from the same human subjects, and subsequently killed by an

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The Lancet · Saturday 5 November 1960

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PROGNOSIS AND NTICOAGULANT PROPHYLAXIS AFTER CORONARY OCCLUSION

J McMichael
M.D Edin., F R.C.P , Hon F.A.C.P , F.R.S
PROFESSOR OF MEDICINE
E H. O Parry
M.B Cantab , M.R.C.P
MEDICAL REGISTRAR *

DEPARTMENT OF MEDICINE,
POSTGRADUATE MEDICAL SCHOOL, LONDON, W 12

HE outlook after myocardial infarction has usually 1 assessed by comparing results of treatment in a few e patients with a simultaneous control series The ively small numbers in clinical trials (and in a disorder uch variable course 100 must be regarded as small), lead to chance results which are deceptive. In most he trials unequivocal diagnostic criteria have been anded, and these have usually been the characteristic ires that have been recognised for the past thirty s A positive diagnosis is almost irrefutable, and the errors are those of omission (Paton 1957) The ies of Björck et al. (1958) do not support the idea that at improvements in finesse of diagnosis have added nts with improved survival prospects Before long- anticoagulant therapy was introduced there were v studies on prognosis, and to neglect them would be obbish ' (Björck 1960)

e begin by reviewing the more important of these w-up studies to reveal the factors on which prognosis depends We are not concerned with the vexed problem of immediate mortality in the acute phase (Morris et al 1952), but with the survival prospects of those who have recovered from a single recognised acute infarction Though we shall mention some studies which deal with first or subsequent infarctions, and some which include angina, these are mainly used to provide supporting data on certain aspects

Wider appreciation of the methods of calculating life-tables has compelled the discarding of many older studies where survival was estimated on patients who had died, and the recalculation of others such as the data of Sigler (1951) who tabulated the dead and living separately Other papers were discarded because of inadequate information on important influences such as age

Factors Influencing Prognosis

The more important studies on prognosis are summarised in tables 1a, 1b, and 1c, and are illustrated in figs 1 and 2 The studies on myocardial infarction total 5398 patients, while the series including angina adds another 8639 While five-year survival tends to cluster round 65–70%, it will be shown that survival is much better in younger patients who have made a good recovery and worsens with increasing age in those with extensive lesions, and with complicating conditions like hypertension and diabetes

Age and Sex

There is a striking difference between survival prospects in Waldron and Constable's (1950) series and those of Eckerström (1951) the average age in the former was 51 5 but the average age (66 7) of the latter series was obviously weighted by a substantial number in the eighth decade or over Inspection of table 1 shows a general trend to higher five-year mortality

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ent address Department of Medicine University College Hospital, adan Nigeria

TABLE 1a—PROGNOSIS AFTER SURVIVAL FROM THE FIRST MYOCARDIAL INFARCTION

Author	Patients		Start of follow-up	Percentage survival									
	Number	Mean age		1	2	3	4	5	6	7	8	9	10 (years)
s et al. (1952)	123	54	1 month	96		90		83					
and Marks (1953)	166	51·5	Disability benefit	93	84	81	76	70	67	63	58	54	53
(1953)	85		2 months	88		71		64					53
t al (1954)	255	57	2 months					67					44
(1956)	211	58	2 months	92	84	75	68	60	54	48	44	40	37
der and Levander (1959)	232	57	End of 1st admission					58					
et al. (1960)	427	53	2 months	92	86	79	73	69					
ns et al (1960)	235	62	1 month			69		55					29

TABLE 1b—PROGNOSIS AFTER SURVIVAL FROM FIRST OR SUBSEQUENT INFARCTION

Author	Patients		Start of follow-up	Percentage survival									
	Number	Mean age		1	2	3	4	5	6	7	8	9	10 (years)
ström (1951)	109	66 7	1 month	67	51	41	36	30					
on and Constable (1950)	1551	53	3 months	91	84			69					55
et al. (1956)	126	63	2 months	84				54					18
rds et al. (1956)	162	56 7	1 month					49					31
and and Hougen (1956)	929	63 1	1 month	80	60	55							
y and Trulove (1957)	348	59	2 months	86	76	70	65	61	53	41	38	32	32
k et al. (1958)	246	63	End of 1st admission	83	76	69	63	59		50			40

TABLE 1c—PROGNOSIS IN PATIENTS WITH ANGINA PECTORIS OR INFARCTION

uthor	Patients		Type	Start of follow-up	Percentage survival					
	Number	Mean age			1	2	3	4	5	10 (years)
(1951)	1147	55 8	Angina and infarction	Diagnosis	91	86	82	79	77	
et al. (1952)	6882	55 8	Angina and infarction	2 years after diagnosis	84		70		58	37
(1960)	610	59·6	Angina	Diagnosis of angina	92	88	83	79	74	

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TABLE II—CAUSES OF DEATH

Author	Total deaths in series	Causes of death—as percentage of total in each series				
		Recurrent infarction	Sudden death	Congestive heart-failure	Cerebrovascular accident	Other
Levine and Rosenbaum (1941)	80	40	35	20		5
Katz et al (1949)	52	65 4		19 2		15 4
Sigler (1951)	393	56	14	13	5	12
Cole et al (1954)	171	55		17	7	21
Olsen et al (1956)	87	31	17 5	20 5		31
Richards et al (1956)	160	51*		25		24
Weiss (1956)	142	38 7	19	23 3	7	12
Honey and Truelove (1957)	107	45		33 5		21 5
Björck et al (1958)	489	42		32†	7	19
Juergens et al (1960)	82	34	27	21	7	11
Seim (1960)	372	26	15	23	13	23

* This figure applies to cases described as "coronary insufficiency"

† This figure applies to all cases of coronary heart-disease without evidence of acute infarction

These studies show that the chances of survival following acute infarction can be assessed by consideration of age, sex, economic status, severity of the attack and degree of recovery, and complicating diabetes or hypertension The slightest degree of unintentional bias in the selection of patients for treatment and control groups could profoundly influence the results

Anticoagulant Treatment

The use of dicoumarol and phenindione in the treatment of acute myocardial infarction has been followed by a significantly lower mortality during the acute phase Wright et al (1948) reported the results of the American Heart Association's trial which showed a 24% mortality in the control series compared with a 15% mortality in the treated In patients under 60 the crude death-rates were the same in both groups, but there was less nonfatal thromboembolism in the treated patients They accordingly advocated the use of anticoagulants in the acute phase, especially in patients aged 60 and over Feldman et al (1952) studied 189 patients, and did not find that mortality was reduced, or that thromboemboli were less frequent in a series of treated and control patients matched for age, sex, and cardiovascular status The work of Gilchrist and others in this country (Gilchrist and Tulloch 1956) has established a place for anticoagulant treatment in the acute phase, particularly to reduce thrombosis on the venous side, and subsequent emboli in the pulmonary and systemic circulations That these are the effects of anticoagulants is postulated by Bjerkelund (1957), but he cautiously states that "one is hardly justified in concluding that this form of treatment also prevents arterial thrombosis, including coronary thrombosis itself, which in many respects is thought to be of a different nature and related to other pathogenetic factors"

The claims of improvement in prognosis from acute-phase treatment have led to widespread interest in long-term treatment, but, in the absence of critical and controlled work, it is difficult to define the place of anticoagulants in preventing myocardial infarction Gilchrist (1960) admits that in our present experience, and in the absence of all the desirable evidence, the case for long-

publications shows that—although the results are gen described as favourable—it is exceedingly difficult t the figures given as a basis for a definite concl regarding this therapy"

Control Series

We have shown that the prognosis for survival recovery from myocardial infarction is influence many factors affecting the results of any trial u critically matched in control and treated groups S times published results appear convincing unti control group is analysed Bjerkelund (1957) and M R C (1959) studied patients who were ma accurately, but most other papers are less reliable

Lack of an Adequate Control Group

Keyes et al (1956) showed that mortality of treated patients was 8 4% in four years compared 41% in the same period in the untreated with infarctions No facts are given about the age, se history of either the control or treated group, the fo being two-and-a-half times as large as the group trated patients, suggesting some selection

Tulloch and Wright (1954) studied a very small g (32 patients after the late phase of myocardial infarc with a fifteen-month mortality of 6 2%, but they gav facts about their patients, and so it is impossible to a the results, and, in any case, this mortality does not significantly from the upper range of large untre series (fig 8)

Ensor and Peters (1959) used a "pseudo-cont group—i e, a group of patients who had had antico lants for some time but who had discontinued treatm The only fact given about the patients is the severity myocardial infarction in the treated group, but authors are cautious in their claims as they only r a 79% five-year survival in treated patients ag 70 7% in the "pseudo-controls"

Nichol et al (1958) studied the effect of anticoag treatment in patients with impending infarction,

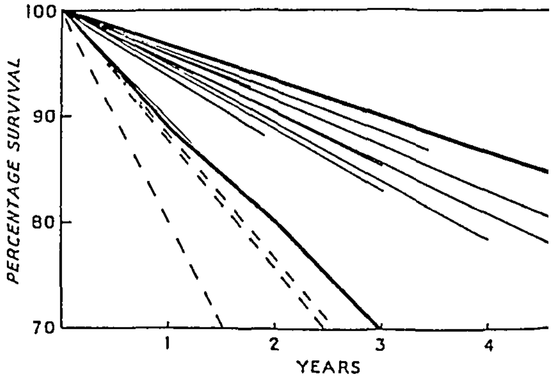

Fig 8—Treated series compared with untreated

The general prognosis derived from fig 1 lies between the lines The survival of treated patients (continuous lines) is s using survival table data or percentage survival at the end o average length of treatment The treated series from above are (1) Tandowsky (1959), (2) Muri (1956), (3) Ensor and P (1959), (4) Suzman (1959), (5) Ødegaard (1958), (6) Tulloch Wright (1954), (7) Bjerkelund* (1957), (8) Waaler† (

with one or two previous infarctions They used controls, however, patients from their records who been previously followed up without any treatment ney also named a group of patients who abandoned -term treatment It is significant to note that 14% the deaths in this group occurred within one month stopping anticoagulants But none of the groups matched and the average period of follow-up in each Their treated patients showed an 88% vival after an average period of 1 87 years, well within ns of past experience (fig 8)

Suzman et al (1955) present formidable figures to that patients on long-term treatment do better than treated during the acute phase only Although this a careful study, the chief drawback to their results is " the final decision for long-term treatment was left the patient " Economic factors obviously entered into selection, and the results of treatment were a five-year val of 76 1% against 45 6% in the untreated cases uzman (1959) has kindly allowed us to see his unpub- figures which show that recurrent infarction ccurred only slightly less often (34 7% against 43 2%), its mortality was less (40 5% against 74 8%) in long-treatment patients than in the short-term group results, however, must be seen against the background of the selection of patients and the age-distribution of the groups, 31% of the patients in the short-term group were over 70, compared with only 20% in the -term group

Tandowsky (1959) does not mention his patients' status, except to describe the 70 controls as " a like group " in whom the mortality (53%) was four times that of the treated (13%), the average duration of treatment was three years and five months

Use of Retrospective Studies to Provide Control Groups

Some papers which have given encouraging figures for urvival in patients treated with long-term anticoagulants not had a concurrent control series Some writers have compared a series of patients treated in one country ith a series reported in a different country some years efore. Thus, Muir (1956) who had a 7 5% mortality an average exposure to risk of twenty-one months ompared his results with those of Parker et al (1946) which were later included in the total series of Block et al 1952), both reporting an exceptionally high (19 and 16% espectively) first-year mortality Waaler (1957) who chieved a 17% three-year mortality, also used as controls he data of Block which are seen to be much worse than hose of Sigler or Seim (table Ic)

Tanzi and van Ness (1957) compared their mortality f 6 1%, in a sixteen-month average, with those " so far eported " Toohey (1958), who had an 11 6% mortality t eighteen months, used as controls patients who had een followed up after myocardial infarction in the same nd another hospital during the seven years before long-erm anticoagulants this series had a 33% two-year mortality Toohey did not mention either age or sex among his patients, and so it is not easy to accept the laim that his results are " statistically significant " His ontrols, who had a much higher mortality than usual, may have been an aged group, and his treated patients were not matched with the controls in any way

dmission to Treated Group and Follow-up Care

Tanzi and van Ness (1957) and Keyes et al (1956) mited their treatment to those who could cooperate The former achieved 6 1% mortality in sixteen months while the latter had a 9 9% mortality between one and thirty-eight months of observation, results which lie within upper range of life expectation as shown in fig 1 The striking five-year survival, 83%, which Morris et al (1952) reported in medical practitioners, demonstrates the part played by intelligence, social status, and careful follow-up in survival after myocardial infarction Constant supervision is certain to ensure earlier treatment of symptoms which may arise, and this is the only way in which the control group of patients in Bjerkelund's (1957) admirable study differed from the treated group The latter were seen every one to three weeks against the three to four monthly intervals between the visits of control patients

Results of Treatment

Although many reports have an inadequate control series, they give valuable facts about survival in the treated patients

Survival of Patients

Many of the earlier papers included a few patients with myocardial infarction, and a larger series treated with long-term anticoagulants for thromboembolic disease, and so are not satisfactory for survival data Tulloch and Wright's (1954) and Muir's (1956) figures have already been discussed Nichol and Borg (1950) treated 78 patients for an average of fifteen months and reported a 15 3% mortality, which is less good than the average (fig 8) Ødegaard (1958) treated 117 patients, of mean age 58 9 for a total of 343 patient-years, and found a mortality-rate of 4 87% per year—a little better than average but not outside the range of untreated patients There was a 10% mortality in 735 patrents with one infarction, studied for an average of twenty months by Nichol et al (1958) they also reported an overall mortality rate of 12% in 1091 patients with impending one or two infarctions, studied for an average of 22 4 months Both these figures are within " untreated " expectation Manchester (1957) expresses his results as the fatality, and number of recurrent infarctions per 100 patient-years, these figures were 0 56 and 2 73 respectively A survival table cannot be made from his data He had twice as many patients with heart-failure requiring digitalis (33%) in his control group as in his treated group (15 6%) The five-year survival of 76% in Suzman's (1959) treated patients may well reflect the better social status of his patients

The chief interest in the reports of Bjerkelund (1957) and the M R C (1959) is the difference which is shown between the control and treated patients during the early months of long-term treatment Bjerkelund (1957) stated that the " force of mortality " seemed to be largest initially in the control group, and that the treated patients—but only those under 60—did not show this initial excess mortality It is noteworthy that in both Bjerkelund's and the M R C series, most of the excess deaths in the controls took place in the first three months after infarction Bjerkelund reported no statistical difference between the " force of mortality " in the treated and control group at any age, a year and more after infarction (see figs 5 and 6 of his monograph) The M R C trial showed a similar trend, and although 19 of the 28 deaths in the low-dosage group occurred in the first six months compared with only 9 of the 17 deaths in the high-dosage group " the difference in the death rate was appreciable only during the first three months of the follow-up period " These results are best demonstrated by the death-rates per 100 man-months of exposure during the first year

Period	*Low dosage*	*High dosage*
Less than 3 months	2 7	0 8
3-6 months	1 7	1 1
6-9 months	0 8	0 5
9-12 months	0 0	0 8

While both these reliable reports show similar results, the efficacy of anticoagulant drugs was only transient Suzman (1959) and Manchester (1957), however, report sustained improvement of prognosis, and so these four important protagonists are far from agreement on the reasons for their advocacy of long-term treatment

No reported series shows that anticoagulant treatment in any way affects the pattern of an increasing mortality with age, or benefits older patients This is thoroughly borne out by Bjerkelund's (1957) results with his older (over 60) patients, whom treatment did not benefit Similarly, the difference between the low-dosago and high-dosage groups of men aged 55 and over was less marked than that in men under 55, which itself did not reach the 5% level of significance (M R C 1959)

These results, and those which have been given above, show that it is probably only in the acute and healing phases of myocardial infarction that anticoagulant treatment may be effective in increasing survival, but even this is not yet statistically proven Long-term anticoagulant prophylaxis beyond about two months after infarction cannot yet be justified by adequate evidence

In small numbers of patients—and we must count the M R C and Bjerkelund series as small—there are obviously possibilities of great variability indicated by "highly significant" results diminishing with the passage of time to statistical "insignificance" in both series That chance could readily operate to account for the results is borne out by the recent work of MacMillan et al (1960) In a statistically randomised series of 27 treated and 23 untreated patients, they had 8 deaths in the treated as against none in the untreated "controls"

Recurrence of Infarction During Treatment

The difficulties of establishing this diagnosis have already been mentioned, and the papers which report the results of treatment are not precise in defining the criteria for a recurrence Bjerkelund (1957) alone classifies his patients into those with definite, very probable, and probable recurrences, and he points out that the diagnosis could not be established with equal certainty in all cases However, the diagnosis of his recorded instances was definite in 63 5% of treated, and in 76% of untreated patients He is careful to state that cases of sudden death were only included as recurrent infarcts if definite signs of a fresh infarct were found post mortem Thus, his criteria differ from those of the M R C report (1959) in which all cases of sudden death were attributed to recurrent infarction Manchester (1957) does not mention the criteria for recognising a recurrence These divergences explain the varying results of table III, where the incidence and mortality of recurrences in treated patients are shown. The apparent tendency towards a lower rate of reinfarction in the treated patients is open to critical doubt on account of the above difficulties of controls and diagnosis.

Certain facts must be emphasised which arise from this study of reinfarction Bjerkelund (1957) makes a thorough study of the "force of recurrence" in his control group and shows a definite "excess of recurrences" in those under 60 during the first six months—but shows that this is not significant in the patients more than 60 years old Moreover, after twelve months he can find no statistical difference between the "force of recurrence in the treated and control groups, and he finds that anticoagulant therapy has not given much protection to those with a high "force of recurrence"—i e, those with a previous recurrent infarction He claims that during the observation period two-fifths of the recurrent infarctions and at least half of the deaths due to recurrences were prevented by dicoumarol treatment His most significant differences, however, were either in the first month of observation (i e, near the acute phase) or in patients over 70

The M R C (1959) data on recurrent infarction differ from those of Bjerkelund in suggesting that a disparity in infarct-rate between high-dose and low-dose patients continues into the second year of follow-up Although there were fewer cases of recurrent infarction among the treated, 17 out of 24 died from their recurrence, against 29 out of 60 in the low-dose group

A reduced incidence of recurrent infarction in treated patients was also reported by Manchester (1957) and his results appear to be formidable evidence, but he did not give details of the patients studied, nor any criteria for the diagnosis of a recurrence A large number (157) of his patients abandoned treatment, and these may have weighted survival in those continuing treatment towards a better prognosis, with fewer recurrences, as the M R C report suggests

Suzman (table III) also found a slightly lower rate of reinfarction in his long-term treated patients, especially in those whose previous infarction had been severe However, the mortality of recurrent infarction was higher in the control group (49 4% against 27 6%) It is noteworthy that the mortality in Suzman's "treated" recurrences was about half that in the M R C series where it was remarkably high (75%) Bjerkelund (1957) found that patients with a mild previous infarction had fewer recurrences, whereas Suzman (table III) found the reverse Recommendation of long-term anticoagulants is thus based on widely divergent findings

TABLE III—RECURRENT INFARCTION IN TRIALS OF TREATMENT

Author	Number of patients		Period of study (years)	Recurrence of infarction			
	Control	Treated		Control		Treated	
				Incidence (%)	Mortality (%)	Incidence (%)	Mortality (%
Keyes et al (1956)	231	121	2	38 0		2 0	
Bjerkelund (1957)	118	119	3	40 (*a*)	41 6	22 (*a*)	34 6
Manchester (1957)	200	204	10	31	53 0	14 2	20 6
Nichol et al (1958)		1091	1 87			10 75 (*b*)	66
Medical Research Council (1959)	188	195	3	27 5	46 5	12 3	75
Suzman (1959)	216 (*c*) mild	55	10	32 8	19 4	34 5	27 6
	298 (*c*) severe	115	10	50 7	61 4	31 8	38 3

(*a*) Includes cases classified as definite, very probable, and probable myocardial infarction
(*b*) Includes cases described as ventricular fibrillation or cardiac arrest (i e, sudden death)
(*c*) Refers to severity of first attack of infarction

eturn to Work

It has already been shown that many patients are able return to work, and to stay at work after recovery myocardial infarction without long-term treatment. is disappointing, therefore, that Bjerkelund (1957) d that only slightly more treated than control patients d to work. The small difference between the two ups probably depended upon more elderly patients among the controls. Bjerkelund states that the "difference hardly gives reason to believe that the treatment has influenced the patient's ability to work." The M.R.C. 1959) found that there were slightly more men at work n the treated group (83% against 71%), but the proportion without dyspnœa was the same (66% and 67%). This s the more remarkable as the 31 of the "untreated" vivors had had an additional recurrent infarction. Muir (1956) reported that 79% of treated patients were work, a figure in agreement with the M.R.C. treated and untreated groups, and thus hardly to be claimed as a erapeutic success.

A patient's return to work will in part be determined by his symptoms. A common symptom which can limit lity to work is cardiac pain, which has been reported be less frequent in patients treated with anticoagulants. We wish, however, to repeat Bjerkelund's (1957) statement that "cases of angina pectoris often have spontaneous fluctuations, and this makes assessment of prophylactic therapy very difficult."

Manchester (1957) found that 38 of 74 treated patients had less cardiac pain, compared with only 20 of 72 control patients. Similar figures were given by Tandowsky (1959) for the abatement of coronary insufficiency, and Waaler (1957) found that 8% of his series of treated patients with angina pectoris were wholly relieved, and 12% were partially relieved of pain. The M.R.C. (1959) reported that the absence of anginal pain uggested a slight superiority among the treated (64% against 2%) over three years of study. Bjerkelund (1957) meticulously ubdivided his patients according to their grade of cardiac ain, but was not convinced that dicoumarol had any "definite" prophylactic effect against this symptom.

Thromboembolism

The prevention of venous thromboembolism after the initial acute phase does not receive much prominence in any report, and it is evident that it is not very important clinically after the acute phase, though when it is recognised, the mortality is high.

Manchester (1957) reported 35 cases (17·5%) of whom 16 45·7%) died in his untreated group, against only 5·8% with 14·2% mortality in his treated patients. Bjerkelund (1957) ound extracardiac thromboemboli in only 2 of his control group, and in none of his treated group. Suzman (1959) ound thromboembolism three times more frequently in his untreated patients. Only 1 case is mentioned with a fatal cerebral embolus in the M.R.C. low-dosage group. It seems ikely that patients on anticoagulants are protected from venous hromboembolism (Sevitt and Gallagher 1959).

There is adequate postmortem evidence, however, that coronary arterial thrombosis can, and frequently does, develop in patients under expert anticoagulant control. Fresh coronary-artery thrombosis was found at necropsy n 58% of Bjerkelund's untreated patients, and, post mortem, in 26% of his treated patients. Capeci and Levy 1959) were not impressed by any diminution of thrombus ormation in treated patients who came to necropsy.

ndications for Treatment

Two different opinions are held about choice of patients or, and duration of, treatment. Nichol and Fasset 1947) decided to use anticoagulants for patients with recurrent infarction. Wright et al. (1954) and Suzman et al. (1955) also reported that this type of patient might benefit from treatment. The M.R.C. (1959) found that a lowering of the infarction-rate appeared most clearly in those in whom the risk of recurrent infarction was high, in younger males, and in those with more than one infarct. On the other hand, Bjerkelund's results indicated that there was no benefit from treatment in patients who had had more than one infarct; he would recommend treating all, or a large number of, patients for six months or a year, but not thereafter. The M.R.C. report, however, recommends that "continuous" treatment should be given as this can make a useful, if limited, contribution in the aftercare of patients who have recovered from the acute phase of myocardial infarction, in spite of their own evidence that the regime is of little value after six months.

Discussion

At the beginning of this paper, we showed that patients who survive the acute phase of a myocardial infarction have a five-year survival-rate of about 66%. This figure has varied according to the type of patient who has been followed up, ranging from above 80% in the doctors studied by Morris et al. (1952) to 30% in Eckerstrom's (1951) elderly patients. We have mentioned the remarkably good five-year survival figures for patients who make a complete clinical recovery, or who are young at the time of their infarction. All this evidence shows that myocardial infarction may often be followed by long survival. The various factors which affect prognosis have been documented in order to give a background of experience against which the results of long-term prophylaxis may be reviewed.

In studying the published reports on anticoagulant prophylaxis, we have become critical of the controls, who have often been at, or below, the lower extreme of prognosis found in untreated patients, while the treated fare no better than those in the upper range of survival prospect (fig. 8). The careful studies of Bjerkelund (1957) and of the M.R.C. (1959) have been a constant source of valuable data, but there is surprisingly little work of similar calibre in other studies.

Despite many claims, the evidence that long-term anticoagulants prevent recurrence, or reduce mortality, after the acute phase of infarction is still inadequate. Most of the benefits reported by Bjerkelund and by the M.R.C. working party occurred in the first few months—i.e., while patients were still recovering from the acute event. If the action of the drugs is to prevent arterial thrombosis, there is no reason why this prophylactic action should cease after a few months, and it may well be that the early benefits reported in the Bjerkelund and M.R.C. series are in fact related in some way to the early healing phase of the actual infarction. Another possibility is of harm to the controls from sudden termination of acute-phase treatment.

It seems possible that most of the benefits which have been reported in the acute phase of infarction are related to the efficacy of the drug in limiting venous thrombosis and preventing pulmonary embolism; most reports are consistent in this respect. The recent studies by Sevitt and Gallagher (1959) on prophylaxis of venous thrombosis with phenindione in patients with fractured femora are most encouraging. The apparent failure of the same measures to prevent coronary occlusion is all the more disappointing. Antiprothrombin drugs have also failed in cerebrovascular occlusive disease (Marshall and Shaw

1960), and in occlusive arterial disease of the legs (Singer and Rob 1960)

Venous and arterial thromboses probably differ considerably in their pathogenesis Venous thrombosis is undoubtedly promoted by stagnation in veins of the calf, often subjected to prolonged mechanical pressure in bed in debilitated patients Arterial thrombosis, on the other hand, is based on underlying disease of the arterial wall—atheromatous plaques and ulcers, which can liberate local tissue thromboplastins into the blood-stream, which in turn may be retarded by upstream narrowing of the vessel Ischæmia and myocardial infarction have been reported in patients with hæmophilia (Boivin 1954, Borchgrevink 1959, Stewart and Acheson 1957) The development of arterial occlusions in these patients reinforces the importance of local release of thromboplastin from the damaged intima as a crucial event in the changes leading to thrombosis, even of hæmophilic blood (Astrup et al 1959) Mural thrombi over infarcts form with almost equal frequency in patients on anticoagulants as compared with controls (Gilchrist and Tulloch 1956) Such observations raise serious doubts on the usefulness of anticoagulants in preventing local thrombosis on damaged arterial intima

Any problematic benefit from anticoagulants in the prevention of thrombosis should be weighed against the considerable risk of hæmorrhage mentioned in most reports Lethal cerebral hæmorrhage occurred in 4 out of 118 patients in Bjerkelund's (1957) series, 2, and possibly 3, fatalities were also recorded from Newcastle (Fuller 1959) Quite apart from the risk of cerebral and other fatal hæmorrhages, morbidity can result from serious bleeding from anticoagulant treatment Anticoagulants may not avert arterial occlusion, and there is a real, and probably increased, risk of thrombosis in the period immediately after the drugs are stopped Various reports have suggested that sudden cessation of antiprothrombin drugs may be followed by arterial occlusion within a short time (Nichol et al 1958), 20 such instances are documented by Dinon and Vander Veer (1960) It is not impossible that this complication may have been responsible for the early high mortality, so near the end of acute-phase treatment, in both the M R C and the Bjerkelund control patients Hence, when anticoagulants have been used in the acute phase of myocardial infarction, their administration should be tapered off over a period of three to four weeks

Finally, it is well to remember that factors other than thrombosis also play a part in the production of myocardial infarction Among them are thickening of the atheromatous plaques themselves, subintimal hæmorrhage (Paterson 1936, Paterson et al 1957), and sudden falls of blood-pressure reducing perfusion of critically narrowed coronary vessels Furthermore, recurrent thrombosis may be responsible for a little more than half the ultimate death-rate in patients who have recovered from a cardiac infarction

Summary

The survival of patients after recovery from myocardial infarction, and the factors which influence prognosis, have been studied from reported series

There is broad agreement in the published data, totalling over 5000 patients (table 1a and 1b), that the prospect of five-year survival in cases under 60 ranges round 66%, being worse with increasing age and complications, and better with improving social circumstances and completeness of recovery

Long-term anticoagulant prophylaxis, as carried today, shows no evidence of improving life when compared with the prognosis in this large of " untreated " patients

Possible reasons for this inefficacy of long-term an coagulant prophylaxis are briefly discussed against background of contrasting mechanisms of arterial venous thrombosis The possibility should also be sidered that some of the early high mortality in " controls may be the result of sudden cessation of " treatment"

We are particularly grateful to Dr M M Suzman and Dr MacMillan for putting their unpublished data at our disposal

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POTASSIUM IN THE TREATMENT OF CHOLERA

RAYMOND H WATTEN
B.A , M D Stanford
ROBERT A PHILLIPS
M.B E , M D Washington, St Louis, B S Iowa
MEDICAL OFFICERS, UNITED STATES NAVAL MEDICAL RESEARCH UNIT NO 2, TAIPEI, TAIWAN (FORMOSA)

Sir Leonard Rogers, in 1909, advocated the use of a hypertonic solution containing sodium chloride, calcium chloride, and 0 4 g (5 4 mEq) per litre of potassium chloride, for the treatment of cholera, but in 1916 he decided to omit potassium from the mixture because ' some physiologists consider it unnecessary and possibly harmful " In 1946, Govan and Darrow demonstrated a fivefold reduction in mortality from infantile diarrhœa when potassium was added to replacement solutions used parenterally Electrolyte studies by the United States Navy in the 1947 Egyptian cholera epidemic showed an excessive loss of potassium in the stools, hence it was recommended that potassium 6 7 mEq be included in each litre of intravenous solution used in the treatment of cholera (Johnson et al 1948) Chakravarti and Chaudhuri, in 1954, recommended giving potassium salts, when the acute diarrhœa of cholera had subsided, to hasten convalescence, providing that renal function was satisfactory Despite the above, a recent review of cholera therapy (Pollitzer 1957) does not mention the use of potassium in the treatment of the acute disease

The Study

During the 1958 cholera epidemic in Bangkok Thailand, eventeen patients with proven cholera were studied intensively during their acute illness For the first 24 hours nothing was allowed by mouth in order to relate the fæcal changes to changes in plasma-electrolyte composition Thus, during the irst 24 hours, fluids were given exclusively by the intravenous route. Meanwhile balance studies were made, and afterwards a diet of boiled eggs, rice gruel, milk, and water was given ad libitum The fæces and urine were collected and measured daily until the patient was discharged. A detailed report of this investigation, including methods and procedures, has been published (Watten et al 1959) While it is impossible from hese studies to calculate balance data for more than 24 hours fter admission, approximate potassium losses during the 2–4 days of diarrhœa may be calculated

TABLE I—MEAN HOURLY FÆCAL VOLUME AND ELECTROLYTE CONCENTRATION OF CHOLERA STOOLS COLLECTED OVER 24-HOURS

—	Volume (ml. per hr)		Electrolytes (mEq per l)			
	Mean	Range	Na	Cl	K	HCO₃
1 patients with fæcal volume over 125 ml. per hr	340	130–730	137	107	16 1	45 2
patients with fæcal volume under 125 ml. per hr	100	23–120	114	89	26 4	43 5

Patients with severe cholera had 24-hour fæcal volumes of –17 litres In these patients the total volume of diarrhœal uid during the 2–4 days of the disease was 10–35 litres During the 24-hour balance period, the mean potassium ontent of the fæces was 16 mEq per litre (table I), and otassium losses in fæces and urine averaged 158 mEq , with range of 50–245 mEq The total fæcal and urinary loss of otassium for the entire period of diarrhœa varied from 400 to 700 mEq , or, for a 50 kg man, the loss was 15–30% of the total exchangeable body-potassium, assuming this value to be 9 mEq per kg body-weight for a normal man (Edelman and eibman 1959)

Fæcal potassium concentrations vary inversely with fæcal volume (Watten et al 1959) Table I shows that patients with fæcal volumes in excess of 3 litres per day (125 ml per hour), had fæcal sodium and chloride concentrations which were nearly isotonic with those of the plasma, while the potassium and bicarbonate concentrations were higher than the plasma levels

With amelioration of diarrhœa and decrease in fæcal volume, the potassium concentration increased while the sodium concentration decreased, this is related to selective reabsorption of sodium in exchange for potassium in the lower ileum and large bowel, and it has been demonstrated experimentally by D'Agostino et al (1953) Paralytic ileus, with abdominal swelling and cessation of diarrhœa, was often seen in patients whom we studied during the 1958 Bangkok cholera epidemic

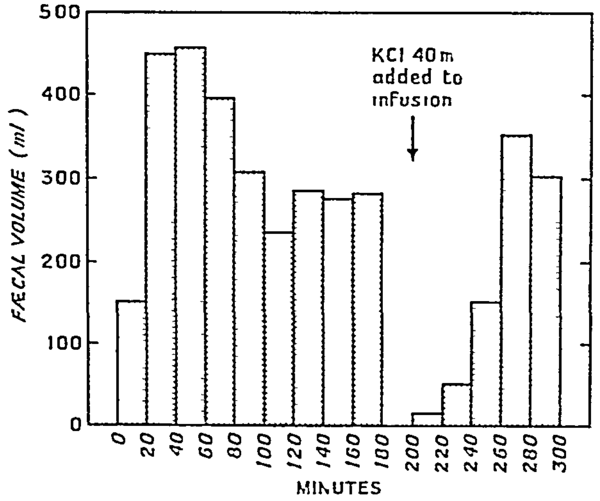

Fig 1—Fæcal volume measured at 20-min intervals during constant infusion (15 ml per min) of normal saline (4-140 min) and 2% sodium bicarbonate (140-240 min)

This complication, as Wilkinson (1943) pointed out, is probably responsible for the rare examples of so-called cholera sicca, in which death results from massive transfer of fluid into the bowel lumen without diarrhœa

Fig 1 shows 20-minute fæcal volumes in a patient during infusions of normal saline and 2% bicarbonate solution The drop in fæcal volume at 180 minutes was probably the result of potassium deficiency, because balances at that time revealed a loss of 165 mEq of potassium Fæcal volume increased after infusion of 40 mEq of potassium chloride, and then it remained constant with additional infusions of potassium The sequestration of a large volume of diarrhœal fluid in the bowel, caused by paralytic ileus, can be misleading and dangerous if fluid therapy is based on replacement of observed fæcal volume alone Utilisation of more accurate measurements of dehydration, such as plasma-specific-gravity determinations (Phillips et al 1950) will prevent such errors

During our cholera studies, alkalosis developed after treatment in four patients who had been given only 20–80 mEq of potassium (replacing about 10% of the deficit) during treatment (table II) The plasma-CO_2 content remained above 30 mEq per litre for as long as 7 days after the diarrhœa

TABLE II—ADMISSION AND CONVALESCENT PLASMA-CO CONTENT AND POTASSIUM LEVELS IN FOUR PATIENTS WITH SEVERE CHOLERA

Patient no	24-hr fæcal volume (ml per hr)	Plasma CO content (mEq per L plasma-water)		Plasma-potassium (mEq per l plasma-water)		Interval (days)
		Admission	Convalescent	Admission	Convalescent	
2	476	22 2	29 3	4 5	3 8	7
10	235	14 0	37 0	4 8	3 3	6
12	302	11 1	30 4	4 3	3 1	3
15	725	20 5	33 3	4 9	3 4	7

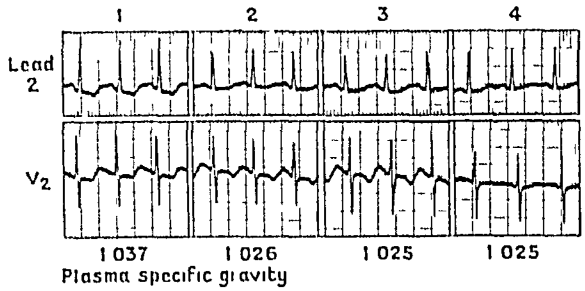

Fig. 2—Patient no. 6, 30-year-old Thai woman, 24-hour fæcal volume 7700 ml.

The tracings were made (1) on admission at 12.30 A.M. (plasma-CO_2 content 15 mEq. per litre), (2) at 2 P.M. after rehydration with 3 litres of normal saline, (3) at 4.30 P.M. after infusion of 500 ml. of 2% sodium bicarbonate solution (which raised the plasma-CO_2 content to 22 mEq. per litre), and (4) at 5.30 P.M. after infusion of 10 mEq. of potassium chloride in 1 litre of normal saline.

ceased, despite a normal diet. The data were not complete enough to indicate the pathogenesis of alkalosis associated with potassium deficiency in cholera, but they do indicate that a moderate alkalosis developed in several patients with serious potassium depletion, who had been treated with adequate quantities of saline and bicarbonate.

Serial electrocardiograms were taken during treatment of thirteen patients, but only five showed definite evidence of potassium deficiency either before or after the dehydration had been corrected with saline. Fig. 2 shows the changes in a patient with severe cholera. During the 5 hours before admission this patient passed seven watery stools, and was moderately dehydrated. The first tracing, taken 6 hours after the onset of the patient's diarrhœa, showed T-wave alterations in all leads. T-wave changes were less pronounced after saline and bicarbonate infusions, but they did not return to normal until potassium had been given. These changes were not caused by dehydration because plasma-specific-gravity values were within the normal range during the infusion therapy.

Discussion

Rational treatment of cholera requires knowledge of the altered physiology and chemistry of this disease. Such information has not been available until recently (Watten et al. 1959), and consequently therapeutic regimens have changed little since Rogers' recommendations of 50 years ago. There is universal agreement on the necessity for prompt replacement of water and salt, and the use of bicarbonate for the treatment of acidosis is accepted, but the risk of pulmonary œdema from overhydration (Chaudhuri 1950, Chakravarti and Chaudhuri 1954) is emphasised far more often than the danger of insufficient fluid replacement. Myocardial depression caused by potassium depletion rather than by rapid replacement of fluid may well be the important factor in the genesis of this complication. Death from "heart-failure" during convalescence (Baligh 1918) may also be due to deficit of potassium. Moreover, adjuvants to therapy (colloid plasma-volume expanders, cardiac stimulants, vasopressor agents, bacteriophage, antibiotics, &c.) continue to be given emphasis out of proportion to their value, and they detract from what should be the main line of cholera therapy—i.e., replacement of the lost water and electrolytes.

A lesser-known result of potassium depletion is renal tubular damage; vacuolisation of distal tubular cells, and damage to the collecting tubules, have been reported (Relman and Schwartz 1958, Holliday 1959). In a recent study of patients dying in uræmia after cholera, Benyajati et al. (1960) found microscopic changes in renal structure similar to those produced by potassium depletion. Ischæmic renal damage and uræmia due to delayed or inadequate fluid replacement is a frequent complication of cholera. Damage to kidney structure and impairment of function produced by potassium loss may contribute to renal failure in these cases.

Neuromuscular disturbances are a well-known complication of potassium deficiency. But there is only one report of transient potassium-depletion paralysis following cholera in eleven convalescent patients, this promptly subsided after potassium-chloride infusions had been given (Huang and Mao 1947). Instances are known of "secondary collapse" involving weakness, muscular twitching, and tetany during convalescence from cholera (Dr. C. Benyajati, personal communication).

Although plasma-potassium levels will eventually reflect potassium deficits, determinations made during the acute phase of cholera are of no value in establishing the need for potassium replacement. Data from our studies (Watten et al. 1957) indicate that plasma-potassium levels in acutely dehydrated patients were within the range of normal when corrected for plasma-protein concentration (expressed as mEq. per litre plasma-water). Furthermore, plasma-potassium values after rehydration were also within the range of normal. These findings indicate, as Scribner et al. (1958) concluded, that plasma-potassium concentration is independent of the volume of the extracellular space.

Saline solutions have been the foundation of cholera treatment. Table I shows that, for each litre of fæces lost from a patient with severe cholera, a litre of approximately isotonic saline will replace the salt lost. Theoretically, each litre of replacement solution should also contain about 16 mEq. of potassium and 45 mEq. of bicarbonate to replace these electrolytes.

The amount of potassium required to replace the deficits in acute cholera should be sufficient to prevent complications without producing toxicity. Ideally, measured potassium losses in urine and fæces would be exactly replaced, but facilities for this are rarely available in areas where cholera remains a problem, and even if they were the demands on time, personnel, and the laboratory during an epidemic would preclude their use except in the exceptional patient.

It therefore seems advantageous to add a small amount of potassium to each bottle of replacement solution. But the rapid infusion of 3–4 litres of a potassium-containing solution during the initial treatment of shock and collapse might increase the plasma-potassium levels too much, with the danger of heart-block and other conduction defects. Until further information is available it is advisable to use parenteral potassium only after the initial dehydration has been treated, and when maintenance solutions are given more slowly.

For the treatment of potassium depletion in infantile diarrhœa, Govan and Darrow (1946) recommended a solution containing 35 mEq. of potassium per litre which he never gave at the rate of more than 120 ml. per hour. In adults, Nadler et al. (1950) reported no untoward effects in treating the potassium depletion of diabetic acidosis and prolonged vomiting with an isotonic solution of potassium chloride (155 mEq. per litre) given intravenously at a rate of 290 ml. per hour (45 mEq. potassium per hour). But these infusion rates are far less than we have found necessary to maintain hydration in cholera patients, and an infusion-rate of 100 ml. per minute is for the rapid treatment of collapse during the period of rehydration

Without electrocardiographic or laboratory control, which is impossible during the treatment of large numbers of acutely ill cholera patients, a solution is needed that is safe under a variety of conditions. The addition of 10 mEq. (7.5 g.) of potassium chloride to 1 litre of saline should satisfy this need, and during an epidemic this solution could be used with safety in remote areas, even without medical supervision. It will replace at least half the initial potassium deficit in the average severe case, and it should prevent the major complications of potassium deficiency. As long as diarrhœa continues 10 mEq. potassium may be added to each litre of maintenance solution with impunity, even when the renal function is unknown, because potassium will continue to be lost in concentrations of 10–50 mEq. per litre of fæces (Watten et al. 1959). With cessation of diarrhœa, if renal function is not satisfactory, potassium should be discontinued. In uncomplicated cases, 10 ml. of a palatable mixture containing 100 g. each of potassium citrate, potassium acetate, and potassium bicarbonate per litre of water may be diluted and given by mouth three times a day as soon as nausea and vomiting cease.

From the electrolyte data reported in this paper, and from knowledge of experimental and clinical potassium depletion, one can conclude that the recommended addition of potassium should provide a more physiological approach to cholera therapy, diminish complications, and further reduce the mortality-rate.

The opinions and assertions contained herein are those of the authors and they are not to be construed as official or as reflecting the views of the Navy Department or the Naval Service at large.

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> “One of the explanations why people in general are rather well satisfied by living and working in these regulated national communities of the Western World is undoubtedly that they do not notice the controls so much, or do not react so violently, as they are becoming accustomed to them. The present level of taxation in all Western countries, for instance, would have been unthinkable fifty or even twenty years ago. There is a deep truth in Albert Einstein's observation that if there were beings who were flat and without thickness and who lived on the surface of a sphere, they would have no idea of a third dimension. Like domesticated animals, people growing up in the Western type of regulated national communities have no real conception any longer of a wilder life. To the reflecting social scientist the adaptability of the human animal to new conditions will never cease to be one of this world's wonders.”
> —GUNNAR MYRDAL. *Beyond the Welfare State*, London, 1960.

FALLACIES IN INTERPRETATION OF QUECKENSTEDT'S TEST

A. R. TAYLOR
M.A., M.B. Aberd., F.R.C.S.E.
NEUROLOGICAL SURGEON, ROYAL VICTORIA HOSPITAL, BELFAST

IN 1916 Queckenstedt introduced his test for the detection of spinal subarachnoid obstruction. He noted that compression of the jugular veins caused a “congestion of the brain”, and consequent increase in the cerebrospinal-fluid (C.S.F.) pressure. In the presence of an expanding spinal lesion sufficient to block the subarachnoid space, this increase is not transmitted to the spinal canal, and is therefore not reflected in the fluid level of a lumbar manometer. Queckenstedt wrote of congestion of the brain. Had this conception been retained, and not replaced, as it was, by that of increased intraventricular pressure, later confusion might have been avoided. As the original test was modified, and combined cisternal and spinal puncture methods were introduced to define the site of obstruction more precisely, inaccuracies in the interpretation of results appeared.

The first refinement was added by Ayer (1921) who, having perfected his technique of cisternal puncture, used it in combination with lumbar puncture to show a rise in cisternal pressure without a coincident lumbar increase as additional evidence of spinal obstruction.

About 1924, at least three workers—Fremont-Smith, Cushing, and Eskuchen—independently described a method of combining ventricular with lumbar puncture to confirm the diagnosis of posterior-fossa obstruction, but here conditions are dissimilar to those in the spinal theca, and the test thereby becomes less reliable.

Further improvements in detail were added. Poppen and Hurxthal (1934) pointed out that before evidence of block is manometrically apparent, the subarachnoid obstruction must develop to a degree in which the area left for fluid circulation is less than the area of cross-section of the spinal-puncture needle. Stookey and Klenke (1928) placed the test on a firmer mathematical and mechanical basis by explaining the delayed rise and the rise maintained after removal of jugular compression. Grant and Cone (1934) applied graduated pressures to the neck by a manometer cuff in steps of 5 and 10 mm. Hg and recorded them, with successive C.S.F.-pressure readings, on a chart. This obviated the individual variants of degree and site of finger compression, and gave comparable records compiled by different observers.

Antoni (1931), at the Copenhagen clinic, modified the combined cisternal and spinal test. He postulated that, as the superior caval venous pressure decreased with the inspiratory expansion of the thoracic cage, and the inferior caval venous pressure increased with the descent of the diaphragm, the cisternal level should fall and the lumbar pressure rise with each inspiration, if a block existed between the needles. Wagner (1947), reporting over 800 double punctures from the same clinic, concluded that the test for “respiratory block” was not reliable, because the communicating vertebral venous system equalised the pressure between the superior and inferior caval systems.

In the “reversed Queckenstedt test” saline is injected into the sacral epidural space, raising the pressure at that level. The absence of a corresponding rise at a higher lumbar site signifies subarachnoid obstruction between the two needles.

As a result of these combined methods, many observers, instead of thinking in terms of venous distension causing increased pressure, thought instead of columns of C.S.F. moving from one part of the cerebrospinal axis to another. For example, Elsberg (1941) said: “The compression of the jugular veins causes a venous congestion within the cranial cavity, and as a result, the expulsion of C.S.F. from

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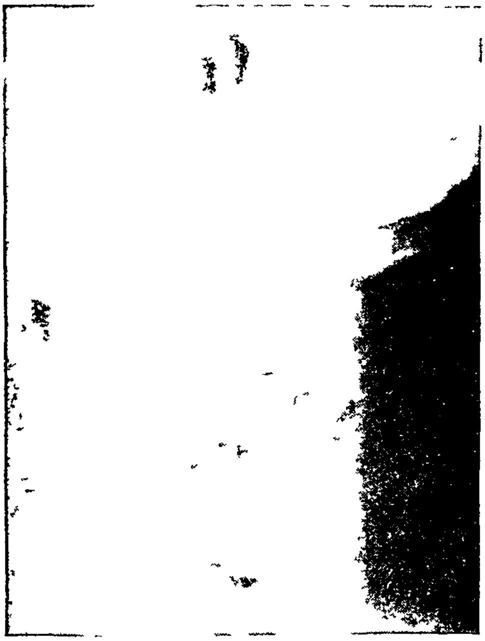

Fig. 1—Injection into the internal jugular vein of a living subject with both jugular veins compressed.

Contrast medium is seen filling the vertebral venous systems of the same side as far as the lower cervical region.

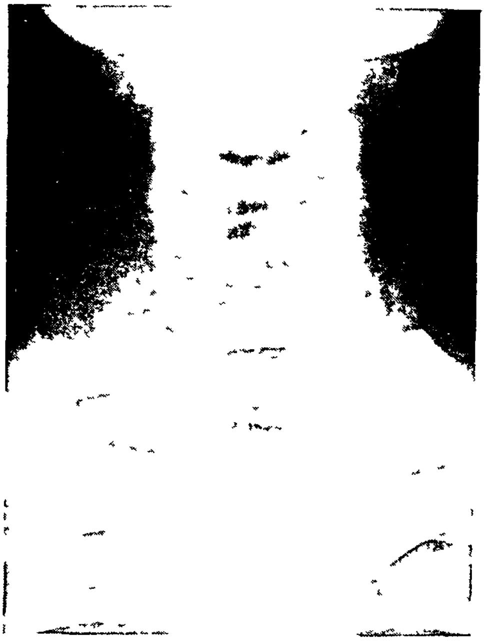

Fig. 2—Injection into the jugular bulb in a cadaver with jugular veins compressed.

The vertebral venous system is filled on both sides to the lower cervical level.

the ventricular cavities." This misconception of rising ventricular pressure was encouraged by Dandy and Blackfan's (1914) theory that the rise in C.S.F. pressure was caused by congestion of the choroid plexuses and increased fluid production in the ventricles. Becht (1920) disproved this by showing that C.S.F. pressure returned to its initial level within 11 seconds after release of jugular compression, but took 6 minutes to return after the volume of C.S.F. was increased by the subarachnoid injection of saline.

That venous and C.S.F. pressures move in parallel was shown by Weed and Flexner (1921) in dogs, the fluid pressure increase bearing an almost constant relationship of 65% to the venous. Bedford (1935) confirmed this. In looking for the explanation of apparent anomalies in the results of Queckenstedt's test, attention must be focused on the changes attending intracranial venous distension as such, rather than those attending a rising C.S.F. pressure in the ventricles, or elsewhere in the cranial cavity.

Evidence for Posterior-fossa Obstruction by Queckenstedt's Test

After the introduction of ventricular puncture, some workers—e.g., Gardner (1928) and Smyth and Henderson (1938)—sought to show that, on jugular compression, pressure rose higher in the ventricle than in the spinal canal if there was obstruction in the posterior fossa.

O'Connell (1943) drew attention to the fact that rise in pressure, measured through a wide-bore ventricular needle was much more rapid than through a narrow-gauge spinal needle, and that pressure rises in manometers connected to ventricular and spinal needles should not be directly compared.

To eliminate this error, recordings were made of a series of combined ventricular and lumbar punctures, using a blunt fine-bore ventricular needle of the same gauge as the lumbar one. Jugular, thoracic, and abdominal compression were successively performed, and manometer readings were recorded in the ventricle and spinal theca. The series observed included some patients with normal intracranial pressure, and others with proven obstruction at the tentorium and aqueduct, or at the foramen magnum. In none of these did the ventricular pressure rise higher or more rapidly than the lumbar pressure. There was apparently some mechanism whereby pressure was equalised throughout the cerebrospinal axis even when the pathways were obstructed. That this mechanism resides in the vertebral venous system is seen at surgical exposure of the posterior fossa.

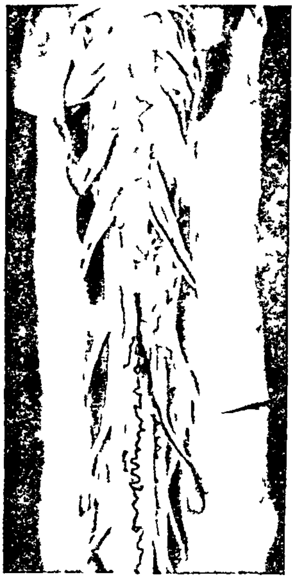

Fig. 3—Spinal canal in the injected cadaver filled with dye to C7.

When jugular pressure is applied, there is a rapid outflow of C.S.F. from the fourth ventricle, and the cerebellum is displaced downwards, but, in addition, there is distension of the whole venous bed in the posterior fossa and in the visible upper region of the cervical spinal canal. Plainly, therefore, a rise in pressure caused by distending this venous bed will be transmitted to the C.S.F. pathways whether there is obstruction at the tentorium and fourth ventricle or not. Outflow of C.S.F. from the fourth ventricle may be impeded, but displacement of venous blood into the cerebellar and spinal veins will not. Obstruction in the posterior fossa may sometimes

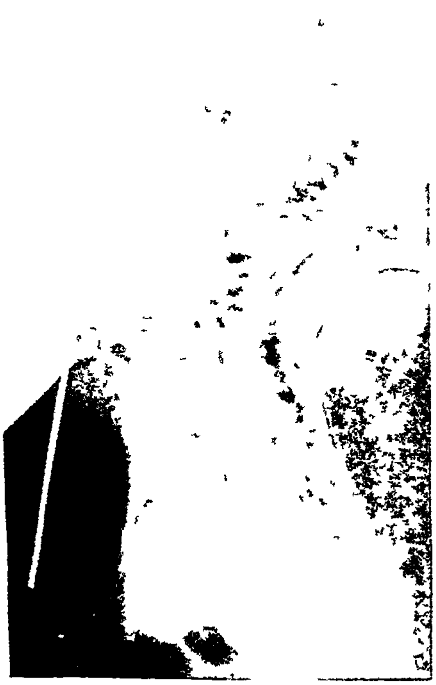

Fig 4.

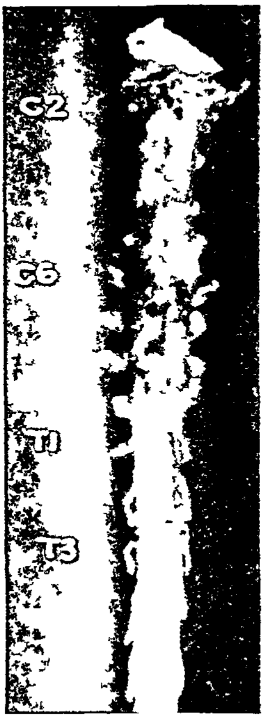

Fig 5

Fig 4—Injection into jugular vein of a rhesus monkey with all jugular veins tied off

Dye fills the vertebral venous system and escapes to the innominate veins at the lower cervical level

Fig 5—The monkey's spinal cord, showing the level of venous filling

delay the rise of fluid in a spinal manometer on jugular compression, but it will not prevent it.

Obstruction in the Cervical Canal

A negative Queckenstedt test in the presence of obstruction in the cervical C.S.F. pathways is less easily understood, but has often been described

Symonds and Meadows (1937) analysed seven cases of tumour at and below the foramen magnum. In none was a complete manometric block demonstrated, although in four the rise or fall was described as being a little delayed. In the one case in which a satisfactory myelogram was obtained, complete spinal block was demonstrated. These workers were led to conclude that "the degree of subarachnoid block, in relation to the severity of the clinical symptoms, would appear to be less in these cases of high cervical tumour than it is at a lower level" It is more likely that the degree of subarachnoid block is as great, but the methods of detecting it are subject to error

Martin and Kleyntjens (1950) described three lumbar punctures performed on cases of meningioma at the foramen magnum. Two showed a slow rise and fall of pressure, and one had normal responses to jugular compression. They said "Queckenstedt's test shows little, a complete block being quite exceptional"

Weinstein and Wechsler (1940) described a dermoid tumour in the foramen magnum in which the Queckenstedt responses were normal Congenital deformities in this region may also cause spinal obstruction Gustafson and Oldberg (1940) described four lumbar punctures in their series, two partially blocked and two without evidence of block.

List (1941) recorded five cases of platybasia, four partially blocked and one quite free as judged by spinal manometry In the last case the spinal cord was reduced by pressure to a fibrous-looking band of small calibre

I have observed seven cases of neurinoma or meningioma between C1 and C4 in which subarachnoid obstruction appeared to be complete at myelography or operation, although Queckenstedt's test was negative

Experimental Evidence

It seemed likely that, as in the posterior fossa, the obstruction was being bypassed by transmission of increased venous pressure through the vertebral plexuses Evidence in favour of this hypothesis was collected from venous-injection studies in man and animals

A catheter was inserted into the internal jugular vein of patients undergoing carotid angiography With both jugular veins occluded on the cardiac side of the catheter, injections of contrast material were made. Fig 1 shows the intracranial venous distension spreading into the internal and external vertebral venous plexuses as low as C6–7 Injections of barium and dye into the jugular veins of cadavers cephalad to the point of venous obstruction confirmed this X-rays showed a similar filling of the vertebral venous system (fig 2), and the spinal canal was shown to be filled with dye as far as C7 (fig 3)

Similar injections were made in monkeys after tying all the jugular veins X-rays showed the filling of the vertebral veins and the escape back to the innominate veins and the heart (fig 4) The cord and dura preparation shows that the vertebral venous plexus filling extended, as in the human subjects, to the level of the lower cervical spinal canal (fig 5)

Provided, therefore, that a cervical spinal tumour does not obstruct the extradural as well as the intradural spinal veins, jugular compression will cause distension of the vertebral venous plexus as low as C6–7, with compression of the theca below the obstruction and a rise in pressure at the lumbar manometer This rise may not be as great as that normally produced by this distension plus the C.S.F. displaced from within the skull to the spinal canal and thence to the manometer, but it may be sufficient to deceive even an experienced observer (And in the event,

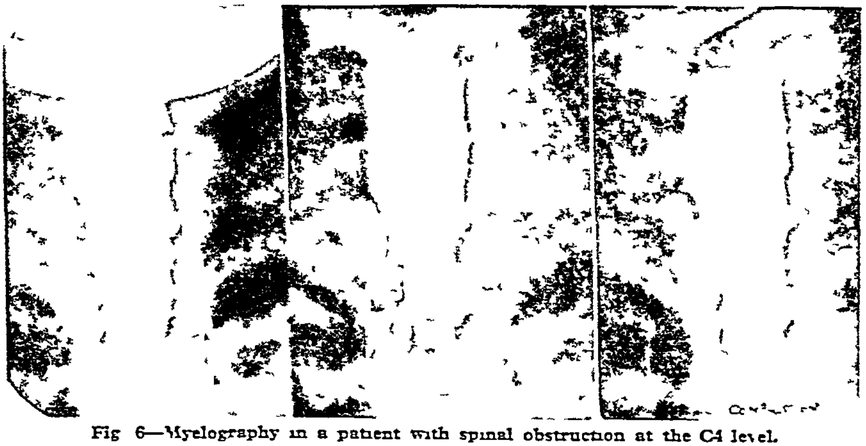

Fig 6—Myelography in a patient with spinal obstruction at the C4 level.

Compression of the jugular veins causes distension of the extradural veins, which narrows the spinal dural canal and causes the oil column to move cephalad.

most lumbar punctures are delegated to the inexperienced) This conception is very important for the understanding of C S F mechanics, because many theories about spinal pressures in Queckenstedt's test have been based on the elasticity or otherwise of the dura, which was presumed to be expanded by the increase of C S F, volume within If the theca is compressed from without in the presence of cervical spinal obstruction, it clearly does not matter whether the dura possesses elastic properties or not If pressure changes are transmitted past a spinal obstruction by extradural venous distension, myelography in such a case should show the oil column narrowing and moving cephalad on jugular compression Fig 6 shows that this does in fact occur

Discussion

The elaborations of Queckenstedt's test by combined puncture methods led to attention being concentrated on changing C S F pressures rather than changing venous pressures The realisation that C S F and venous pressures move in parallel did not help, because observers came to think in terms of increased ventricular pressure being transmitted via the aqueduct to the cisterna magna and the spinal canal in one continuous wave, with obstruction at any point halting the wave As a result, it has been suggested at different times that Queckenstedt's test could help in the diagnosis of aqueduct stenosis, acoustic neurinoma, foramen-magnum tumour, or obstruction of a ventriculocisternal (Torkildsen's) tube The above experiments have shown that it will do none of these things Nor is it a reliable test for cervical spinal obstruction above the level C5–6, unless the extradural as well as the intradural vertebral veins are completely obstructed by the agent compressing the spinal cord A negative Queckenstedt's test should not, therefore, be allowed to cloud clinical judgment in patients showing evidence of cervical spinal-cord compression above this level

Summary

The modifications of Queckenstedt's test are reviewed

Combined cisternal and spinal puncture methods tended to obscure the importance of venous distension as the primary cause of rising cerebrospinal-fluid pressures, as indicated by manometers

Clinical and experimental evidence shows that Queckenstedt's test is unreliable in detecting obstruction of the cerebrospinal-fluid pathways above the C6 level

Acknowledgment is made to Dr W H T Shepherd, of the Royal Victoria Hospital, Belfast, and to Dr Robert Saffley, of the Bangour Hospital, Edinburgh, for their help with the X-ray studies, to the department of microbiology of the Queen s University of Belfast, where the animal experiments were done, and to Mr R G Wood for the photographs

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ANTICONVULSANTS AS A FACTOR IN MEGALOBLASTIC ANÆMIA IN PREGNANCY

P B B GATENBY
M D Dubl, F R C P I, M R C P
VISITING PHYSICIAN, ROTUNDA HOSPITAL, DUBLIN,
PHYSICIAN, MEATH AND DR STEEVENS' HOSPITALS, DUBLIN,
PROFESSOR OF CLINICAL MEDICINE, TRINITY COLLEGE, DUBLIN

THERE have been many reports of megaloblastic anæmia induced by anticonvulsant drugs—an association first described by Badenoch in 1954 The relevant literature is well summarised by Hawkins and Meynell (1958) This anæmia has followed the administration of phenobarbitone and phenytoin, and also primidone In 1956, Girdwood and Lenman drew attention to the similarity in chemical structure between folic acid and these compounds They suggested that these drugs interfered with folic-acid metabolism This was confirmed to some extent by Chanarin et al (1958) who studied a patient in whom megaloblastic anæmia developed after primidone therapy They found that both the absorption and storage of folic acid in the tissues were normal and concluded that interference with tissue metabolism rather than deficiency of folic acid was the cause of the anæmia Recently a similar condition was described in a case treated with phenobarbitone (Chanarin et al 1960) Hawkins and Meynell (1958) investigated the incidence of macrocytic anæmia in large numbers of epileptics who were being maintained with these drugs, and found that this complication was rare Macrocytosis was common, however, in these patients, and 45% of those receiving phenobarbitone and phenytoin showed this feature This macrocytosis could be corrected with folic acid

Megabloblastic anæmia in pregnancy is now being recognised more often, and many reports have been analysed by Chanarin et al (1959) In the same paper, these workers produced evidence of a folic-acid deficiency in two-thirds of those nearing the end of their pregnancy, and in all patients with twin pregnancy All pregnant patients with megaloblastic anæmia were found to have a still greater deficiency of folic acid

Consideration of all these reports suggests that megaloblastic anæmia is more likely to develop when anticonvulsants are used in pregnancy Possible interference with folic-acid metabolism by these drugs is likely to increase the effect of the relative folic-acid deficiency which may occur in pregnancy Though Dimsdale (1959) drew attention to the danger of drug-induced megaloblastic anæmia in epileptics during pregnancy, no report of this complication has yet been found

In a recent survey of 100 cases of megaloblastic anæmia in pregnancy seen at the Rotunda Hospital (Gatenby and Lillie 1960), it was noted that 3 of the cases were epileptics receiving anticonvulsants The incidence of epilepsy in the general attendance at this hospital is approximately 1 in 400, so that the incidence of 3%

TABLE I—ANTICONVULSANTS AND MEGALOBLASTIC ANÆMIA IN PREGNANCY

Anticonvulsant drugs	Number of patients	Number of pregnancies	Incidence of megaloblastic anæmia
Phenobarbitone	28	48	0
Phenobarbitone and phenytoin	7	7	4*
Phenobarbitone and primidone	1	1	0
Methoin (Mesontoin)	1	1	0
No treatment	7	13	1
Total	44	70	5

* 1 unconfirmed

gst the cases of megaloblastic anæmia suggested a ual relationship

The records of all pregnancies in epileptics over a six- period (1953 to 1958 inclusive) were studied 70 ces occurred in 44 epileptics In 7 of them (13) no anticonvulsants were being adminis- , because there had been no attacks for many years case of megaloblastic anæmia occurred in this group The remaining cases were divided into groups depending on the anticonvulsants used Table I shows the relative incidence of megaloblastic anæmia There were no cases in 48 pregnancies treated with phenobarbitone alone There were 4 cases (1 unconfirmed by bone-marrow biopsy) out of 7 treated with phenobarbitone combined with phenytoin

In table II details are shown of the established cases All had severe megaloblastic anæmia which responded briskly to folic acid by mouth, 20 mg daily, in spite of continuation of the anticonvulsant treatment Case C is noteworthy because phenobarbitone alone had been administered in previous pregnancies without the development of megaloblastic anæmia None of these cases had achlorhydria Cases A and B are still under observation and neither has shown radiological evidence of gastrointestinal abnormality

TABLE II—MEGALOBLASTIC ANÆMIA IN PREGNANT EPILEPTICS RECEIVING PHENYTOIN

Case	Pregnancy	1st Hb estimation	Onset of anæmia	Hb at onset	Reticulocyte-peak with folic acid
A	2nd (no treatment during 1st)	11·1 g per 100 ml. at 24th week	6 weeks antepartum	5·8 g per 100 ml.	12% on 5th day
B	1st	8·1 g per 100 ml. at 32nd week	4 weeks antepartum	4·3 g per 100 ml	14% on 6th day
C	6th (phenobarbitone during previous pregnancies)	12·4 g per 100 ml at 24th week	2 days antepartum	6·4 g per 100 ml.	15% on 6th day

Summary and Conclusions

From this analysis, it appears that there is a high incidence (3 out of 7) of severe megaloblastic anæmia when phenytoin together with phenobarbitone is used in the treatment of epilepsy in pregnancy It is recommended that, if phenytoin is being administered to an epileptic during pregnancy, either oral folic-acid supplements should be given during the last trimester, or frequent hæmoglobin estimations should be done to detect the onset of anæmia If it proves to be megaloblastic, it will respond well to folic acid, the anticonvulsant treatment need not be interrupted.

The incidence of megaloblastic anæmia in 57 pregnancies in epileptics receiving anticonvulsant therapy was studied retrospectively There were no cases in 48 pregnancies where phenobarbitone alone was used In 7 pregnancies where phenytoin was used as well as phenobarbitone there were 4 cases (1 unconfirmed) of severe megaloblastic anæmia Folic acid cured the anæmia in these cases, while allowing the anticonvulsant therapy to be continued

I wish to thank Dr E W L Thompson, ex-Master of the Rotunda Hospital, for permission to publish this report of patients who were under his care I am greatly indebted to Dr H. C Moore, pathologist, for his assistance.

References at foot of next column

HYPONATRÆMIA AND IMPAIRED RENAL TUBULAR FUNCTION WITH CARCINOMA OF BRONCHUS

J RUSSELL REES *
M A, M D Cantab, M R.C P
MEDICAL REGISTRAR

S B ROSALKI
M B Lond, M R C.P
REGISTRAR IN CHEMICAL PATHOLOGY

A D W MACLEAN
M B Lond
HOUSE-PHYSICIAN

THE GORDON HOSPITAL AND VINCENT SQUARE LABORATORIES OF WESTMINSTER HOSPITAL, LONDON, S W 1

HYPONATRÆMIA is associated with reduced osmotic activity in the extracellular fluid and may occur with lowered, normal, or increased body-sodium stores It may follow sodium depletion, water retention, or reduction in cellular osmolarity (Schroeder 1949, Sims et al 1950, Rapoport et al 1951, Danowski et al 1955) Renal handling of sodium is variable, and retention or abnormal urinary loss may occur (Rapoport et al 1951, Schwartz et al 1957, Orloff et al 1959)

Hyponatræmia may be found in adrenal failure and severe cardiac, renal, or hepatic disease It has been described in tuberculosis, cerebral disease, and diabetes, and after excessive loss of body secretions by any route (Danowski et al. 1955, Elkinton 1956)

It may develop during acute lobar pneumonia and tuberculosis (Atchley et al 1923, Winkler and Crankshaw 1938, Sims et al 1950) A patient with bronchial carcinoma who showed hyponatræmia and abnormal renal chloride loss was described by Winkler and Crankshaw (1938) Recently, Schwartz et al (1957) reported two patients with carcinoma of the bronchus in whom hyponatræmia and renal sodium loss probably resulted from inappropriate secretion of antidiuretic hormone We describe here a further patient with a bronchial neoplasm and hyponatræmia in whom this mechanism did not operate As well as deficient sodium retention, he had aminoaciduria and increased phosphate excretion The presence of an acquired renal tubular defect is suggested

Case-record

A stoker, aged 53, was admitted to the Gordon Hospital on April 17, 1959 For two months he had suffered malaise, non-productive cough, and loss of appetite, with particular revulsion for sweet and starchy food. He had lost 17 lb, and in the previous fortnight had suffered from nausea, with vomiting on four occasions During the same period he had noted cramps in the abdomen and legs

He had had a dry mouth and increased thirst for a week before admission On April 15, he had fainted, and had since been confined to bed There was no disturbance of micturition, but he had been constipated for a fortnight He had been a moderate pipe smoker for years, and took little alcohol

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* Present address Guy's Hospital, London, S E 1

DR GATENBY REFERENCES

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TABLE I—DAILY INTAKE, OUTPUT, AND SERUM-ELECTROLYTE LEVELS

Day	Sodium intake (mEq)		Fluid intake (ml)		Urine (ml or mEq daily)				Serum (mEq per litre or mg per 100 ml)					
	Oral	I V	Oral	I V	Volume	Na	Cl	K	Na	Cl	K	Blood-urea	Total protein	—
1	0	0	1090	0	810	79	48	23	109	82	3 4	35	6 4	
2	0	0	2160	0	—	—	—	—	111	84	4 5	36		
3	0	0	1920	0	—	—	—	—	—	—	—	—		
4	0	0	1230	0	1380	108	68	57	—	—	—	—		Vomit 360 ml
5	68	0	1860	0	1360	24	16	45	107	78	—	32		Vomit 360 ml
6	102	185	2250	2280	4320	117	177	95	110	77	5 7	35		
7	102	105	2970	3090	2900	128	130	59	121	84	5 6	22		
8	102	185	2010	1980	3360	70	52	12	113	83	1 3	23		
9	102	335	1830	3510	3220	245	280	28	112	80	3 2	24		
10	102	335	1990	3030	1910	168	196	19	123	97	3 9	—		
11	68	300	1590	1650	—	—	—	—	121	95	3 6	21		
12	68	160	750	1140	1140	145	138	34	127	97	4 7	36		
13	69	160	120	1140	1000	122	—	57	126	95	1 3	38	5 4	
14	69	160	510	1140	970	123	159	75	131	91	4 5	—		
15	68	160	510	1140	1200	156	199	79	132	106	1 7	57		
16	68	160	510	1110	1000	74	90	100	—	—	—	—		
17	68	100	1110	750	815	61	86	88	—	—	—	—		
18	136	0	1350	0	700	55	90	82	133	100	3 2	70	5 1	
19	136	0	1980	0	—	—	—	—	136	101	5 0	79		
20	0	0	1500	0	790	53	73	79	142	95	4 3	62	5 1	
21	0	0	1210	0	1040	5	16	125	127	102	4 6	75		

— indicates no measurement, 0 indicates no intake On days 11 and 19, the collection was lost Day 1 is a 12 hour collection (6 P M -6 A M) Day 12 is an 18 hour collection I V =intravenous

Examination

He was thin and wasted There was no clinical dehydration or œdema No abnormal pigmentation was noted B P 100/60 mm Hg Respiratory system fine râles at bases of both lungs, otherwise normal The tongue was furred, but the mouth was not dry

Investigations

Daily serum-electrolyte and blood-urea levels, urine-volumes and electrolyte content, and fluid and sodium intakes are shown in table I and in figure

Blood—Hæmoglobin 15 0 g per 100 ml Erythrocyte-sedimentation rate (Wintrobe) 11 mm in the first hour Total white-cell count 9000 per c mm (neutrophils 70%, lymphocytes 30%) Liver-function tests, serum-amylase, and serum-cholesterol normal Serum-albumin 3 9 g per 100 ml Serum-globulin 2 5 g per 100 ml Random blood-sugar 123 mg per 100 ml Wassermann and Kahn tests negative Serum-alkali reserve (day 13) 24 mEq per litre Serum-alkaline phosphatase 7 King-Armstrong units Serum-calcium 10 6 mg per 100 ml , serum-inorganic phosphate 2 2 mg P per 100 ml (day 2) Serum-calcium 13 3 mg per 100 ml , serum-inorganic phosphate 1 6 mg P per 100 ml (day 14) Serum-creatinine 0 6 mg per 100 ml (day 14)

Urine—Urinary calcium 350 mg per 24 hours Urinary phosphate 480 mg P per 24 hours Urinary creatinine 450 mg per 24 hours (day 14) Urinary aldosterone excretion (Dr R V Brooks) 1 8 µg per day (day 16), 1 7 µg per day (day 17) (normal range 3–8 µg per day with a mean of 5 µg) Steroid excretion is shown in table II

The specific gravity was always within the range 1 010–1 026 No albuminuria Intermittent glycosuria and ketonuria There was no glycosuria after day 13, and no ketonuria after day 18 Paper chromatography of urine for aminoacids (Dr J H Wilkinson) showed (1) a large increase of alanine, glycine, glutamine, histidine, lysine, threonine, and γ-amino butyric acid, (2) a moderate increase of glutamic acid, taurine, and serine, (3) small quantities of valine, leucine, and tyrosine, and (4) traces of methyl histidine and cystine This pattern of generalised aminoaciduria was present up to the time of death

Sputum—No malignant cells

X-ray of chest—Mass in left lung near hilum, with bilateral hilar-gland enlargement Normal pulsation and diaphragmatic movement on fluoroscopy

Isotope studies (Dr J F Zilva, Dr J P Nicholson)—Total exchangeable sodium (day 12) 2510 mEq = 51 1 mEq per kg (normal range 37–56 mEq per kg) Total exchangeable potassium (day 12) 2530 mEq =51 1 mEq per kg (normal range 37 5–61 mEq per kg) Na/K=1 00 (normal range 0 69–0 95) Bromide-space (day 13) 15 9 litres=340 ml per kg , (day 14) 16 3 litres=359 ml per kg (normal range for his build 248–378 ml per kg)

Electrocardiography—Day 1, alternating atrial flutter and fibrillation Fast ventricular rate of about 150 beats per minute with both rhythms Day 5, sinus rhythm, rate 80 beats per minute Tracings otherwise normal

Progress

The history of recent cough and the X-ray findings suggested bronchial carcinoma Severe hyponatræmia (109 mEq per litre) was found on admission and was associated with abnormal renal sodium loss (79 mEq in second half of day 1)

He gradually became worse He was moderately thirsty but too ill to drink unless assisted During the first four days he took sweetened fruit drinks only, and he continued to refuse food throughout the rest of his illness

Adrenal failure caused by bilateral metastatic deposits seemed unlikely with a normal blood-urea, a low serum-potassium (3 4 mEq per litre, day 1), and no pigmentation His blood pressure (95–100/60 mm Hg) was low but this was due to tachycardia, and it rose on day 4 to 120/80, when the arrhythmia reverted to sinus rhythm, though the hyponatræmia persisted (107 mEq per litre) He was so ill that it seemed best to give extra salt and sodium-retaining hormones until more was known of his adrenal function On day 5, oral salt in cachets and intravenous saline were begun (table I and figure), and he was encouraged to drink more He cooperated readily and high intakes were achieved between days 6 and 11 He also took a total of 6 mg fludrocortisone between days 5 and 9 This potent salt-retainer was used to avoid confusion in estimations of urinary steroid excretion which were done at this time Fludrocortisone was stopped as soon as these results were known

With this therapy there was slight improvement, though he remained weak The serum-sodium rose only slowly, and continued to rise when fludrocortisone was discontinued on day 8 and sodium intake was increased Intensive sodium therapy was given up to day 11 by which time the serum-sodium level had risen only to 121 mEq per litre

Between days 12 and 16, water intake was reduced as much as possible to see if this would affect the renal sodium loss as in the cases of Schwartz et al (1957) Sodium supplements were continued, so that he also received 1140 ml fluid daily intravenously, and negative fluid balance was not, therefore, achieved In this period, with an intake of 228 mEq sodium daily, the serum-sodium level continued its slow rise to 132 mEq per litre From about day 12, his condition steadily worsened, with increasing back pain at the level of the lower part of the thoracic spine, and by day 17 he was very ill No more intravenous saline was given, but oral supplements were continued for another 2 days His fluid intake was about

1·5 litres daily. He became emaciated, and bronchopneumonia developed. Finally he lapsed into coma and became clinically dehydrated. There was a terminal rise in blood-urea levels, and the serum-sodium rose to a maximum of 142 mEq. per litre on day 20, though it fell again the following day to 127 mEq. He died on day 22.

Necropsy

At necropsy (Dr. J. S. Cornes) an oat-celled anaplastic carcinoma was discovered, originating in the lingular bronchus, and spreading to the lung, mediastinum, and left supraclavicular lymph-nodes. No other macroscopic spread was found, but histological examination showed infiltration of the liver and spleen by tumour cells.

The kidneys were macroscopically and histologically normal. Histochemical staining (Dr. John Pryse-Davies) showed normal alkaline phosphatase, acid phosphatase, non-specific esterase, succinic dehydrogenase, and lactic dehydrogenase activity. Microdissection (Dr. E. M. Darmady) revealed no abnormality.

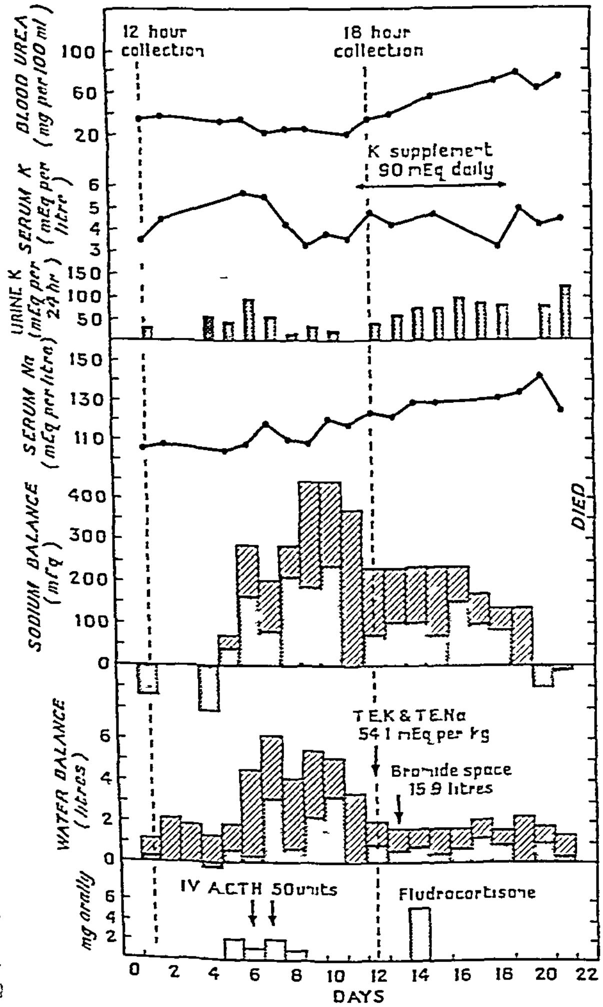
The adrenals were enlarged (combined weight 22 g.) and histologically showed widening of the cortex principally in the zona fasciculata. Histochemical staining (Dr. Pryse-Davies) for alkaline phosphatase, acid phosphatase, non-specific esterase, succinic dehydrogenase, and steroid 3-β-ol dehydrogenase suggested a hyperactive adrenal gland with increased steroid metabolism.

The parathyroids showed slight uniform enlargement. The pituitary contained a small developmental cyst, 3 mm. in diameter, but otherwise was normal.

TABLE II—URINARY STEROID EXCRETION

Day	Urinary steroids (mg. per 24 hours)		Steroid therapy
	17-hydroxy-steroids	17-keto-steroids	
4	17·8	[illegible]	Nil
5	7·7	7·0	Fludrocortisone 2 mg. oral
6	66·0	16·8	Fludrocortisone 1 mg. oral Corticotrophin 50 units I.V.*
7	65·0	21·0	Fludrocortisone 2 mg. oral Corticotrophin 50 units I.V.
9	37·0	11·5	Nil
10	2·1	2·0	Nil
20	17·4	7·7	Nil
21	17·7	18·8	Nil

* I.V. = intravenous.



Water and sodium balance calculated from intake and output figures with no allowance for extrarenal loss or water of metabolism.

Daily intake plotted up from baseline. Daily output plotted down from intake figures. Shaded areas above baseline represent positive balance, shaded areas below are negative balance. Intake data only for days, 2, 3, 11, and 19. For potassium, urinary figures only are shown. T.E.K. = total exchangeable potassium. T.E.Na = total exchangeable sodium.

Discussion

The outstanding feature was the extreme hyponatræmia accompanied by malaise, cramps, and thirst. Mechanisms such as decreased cellular osmotic activity or a new steady state, which have been suggested to explain hyponatræmia in severe illness (Sims et al. 1950, Danowski et al. 1955) did not operate in our patient whose hyponatræmia improved as his clinical state deteriorated.

Addison's disease was not present, nor was there any evidence of the usual type of salt-wasting renal disease which is associated with obvious changes in the kidneys (Stanbury and Mahler 1959). The hyponatræmia was clearly associated, however, with deficient renal sodium retention. This is seen on day 1, and on day 4 when 108 mEq. sodium were excreted after at least 4 days without any salt intake. This sodium-leak was partially inhibited by fludrocortisone on day 5, but the presence of more than a trace of urinary sodium at this low serum-level (107 mEq. per litre) suggests that tubular response was impaired. By day 14, a large dose of fludrocortisone had no effect on sodium excretion showing that the tubular defect had increased.

Aldosterone excretion was reduced on days 16 and 17. By then massive sodium repletion had occurred. Extrapolating from the results on day 12 (allowing 10 mEq. daily for extrarenal loss), total exchangeable sodium is estimated at 2866 mEq. for day 16 (approximately 61 mEq. per kg.) and his serum-sodium had risen to a reasonable level for his clinical state. The low aldosterone excretion at this stage is therefore not surprising.

An estimate of the metabolic state on admission may be made from the isotope studies.

On day 13 the bromide-space was 15·9 litres (within normal limits), and before this marked positive water balance had occurred. Allowing 700 ml. daily as the balance between insensible loss and water of metabolism, a positive balance of 6·2 litres occurred between days 7 and 11. Unfortunately, the urine on day 11 was lost, but the intake makes a negative balance unlikely. Ignoring this day a positive balance of approximately 5·6 litres existed between days 5 and 13. Thus, on day 6, the extracellular fluid volume was estimated at 10·3 litres (about 220 ml. per kg.). This figure would have changed little from the time of his admission, and is abnormally low.

Total exchangeable sodium on day 12 was 2540 mEq. Ignoring day 11 again cumulative sodium retention from day 5 to day 12 was 972 mEq. The amount of food taken was negligible, and allowing 10 mEq per day for extrarenal sodium loss, the estimate for total exchangeable sodium on day 5 was, at most, 1640 mEq (approximately 35 mEq per kg)—an abnormally low figure Total exchangeable potassium on day 12 was 2540 mEq, and cumulative potassium loss in the previous week was 258 mEq (again ignoring day 11) Allowing 10 mEq daily for unmeasured potassium loss, the total exchangeable potassium on day 5 was estimated at about 2868 mEq (approximately 61 mEq per kg), which is in the upper normal range

Thus it appears that our patient on admission was depleted of sodium with a reduced extracellular-fluid space

In their two patients, Schwartz et al (1957) thought that carcinoma in some way caused inappropriate secretion of antidiuretic hormone This produced sodium loss by increased glomerular filtration and, because extracellular volume did not fall, by a failure of aldosterone secretion to rise with sodium depletion Both patients had severe hyponatræmia, in one case as low as 103 mEq per litre, with few symptoms In one the extracellular volume was measured, and was found to be raised

In our patient, the low estimate for extracellular space on admission makes it unlikely that inappropriate secretion of antidiuretic hormone caused his sodium loss The increased thirst in the week preceding admission is in keeping with this view, though thirst can occur with an increase in body water (Wynn and Rob 1954)

The effect of water restriction (days 12–16) was unimpressive There was no dramatic reduction in urinary sodium loss as in the patients of Schwartz et al (1957) and though restriction of water was not severe, it was more than was needed in one of their cases to reverse sodium loss Administration of large amounts of fluid caused improvement, rather than deterioration, and sodium given in this phase was largely retained in contrast to the results in their patients The poor response to salt-retaining hormones is a further point of distinction, and in addition our patient probably produced hypotonic urine on some days (e g, day 8, table I) when specific gravity was not recorded, whereas in the cases of Schwartz et al (1957) urine was hypertonic to plasma

In our patient, it seems that the renal sodium leak was due to impaired tubular function With liberal intakes, sodium loss was not excessive, and repletion was easily achieved However, when sodium intake was low, an obligatory renal salt-loss was revealed, leading to sodium depletion and, eventually, hyponatræmia

This defective reabsorption of sodium, together with intermittent ketonuria and glycosuria, suggested proximal tubular damage, and investigation led to the unusual finding of generalised aminoaciduria Other recognised causes of renal aminoaciduria were absent, and there was no evidence of the adult Fanconi syndrome (Wallis and Engle 1957) in which sodium loss, in particular, does not occur Overflow aminoaciduria may be found with increased protein breakdown, and since the plasma-aminoacid level was not estimated, this is a possibility in our patient, though other features favour its renal origin

Impaired phosphate reabsorption and low serum-phosphate levels accompanied the aminoaciduria, providing further evidence of proximal tubular damage The terminal hypercalcæmia and necropsy findings of parathyroid gland enlargement were probably due to secondary hyperparathyroidism

The distal tubular exchange mechanism of potassium for sodium could function normally as shown by falling sodium excretion in the last week, with increased potassium excretion and K/Na ratios, particularly evident on day 21 24-hour creatinine-clearance on day 14 was reduced, and rising blood-urea levels were recorded in the last week, indicating progressive reduction in glomerular filtration This might have reduced the load on the proximal tubules to a level at which they could function competently The resultant fall in distal tubular flow might then allow the efficient cation exchange and sodium conservation seen on day 21 A diminution in proximal tubular load would also explain the disappearance of glycosuria and ketonuria in the week before death

A defect in proximal tubular function was therefore thought to be present, and a similar defect was postulated by Rapoport et al (1957) as the cause of hyponatræmia in their patients with tuberculous meningitis However it remains difficult to explain the urinary composition on days 1 and 4 The metabolic state on admission should have resulted in maximal aldosterone secretion The modest potassium excretion and low urinary K/Na ratio at this time is surprising and, with the poor response to administered steroids, suggests that distal tubular function was also impaired

Summary

Severe hyponatræmia developed in a man of 53 with bronchial carcinoma He showed poor renal sodium conservation which, with negligible intake because of anorexia, had caused sodium depletion

Repletion was easily achieved and fluid restriction did not affect the sodium loss Metabolic studies suggested that, on admission, he was depleted of sodium, with a reduced extracellular-fluid volume

There was no evidence of adrenal failure, and at necropsy the adrenal glands were enlarged and showed signs of hyperactivity

The renal response to fludrocortisone and corticotrophin was poor There was no clinical evidence of any of the usual types of salt-wasting renal disease, and at necropsy the kidneys were normal on detailed histological examination

There was evidence of functional damage to the proximal tubules with generalised aminoaciduria, glycosuria, ketonuria, and increased phosphate excretion Aminoaciduria was constant throughout, but glycosuria and ketonuria were intermittent and disappeared in the last week

The distal tubular exchange of sodium for potassium was active terminally, though perhaps not on admission It is suggested that the sodium loss was mainly due to proximal tubular damage, and that the bronchial carcinoma had caused this unusual derangement of tubular function

We wish to thank Dr R D Tonkin, under whose care this patient was admitted, for permission to report this case, and Dr R I S Bayliss for advice on the manuscript The microdissection of the kidneys was carried out by Dr E M Darmady The urinary amino-acid determinations were performed by Dr J H Wilkinson We are indebted to Dr R V Brooks for the urinary aldosterone assays Details of the adrenal and renal histochemical studies were kindly provided by Dr John Pryse-Davies The results of the isotope studies were provided by Dr J F Zilva and Dr J P Nicholson The necropsy was performed by Dr J S Cornes The figure was prepared by the department of medical illustration, Guy's Hospital

References at foot of next column

POSTPARTUM PRE-ECLAMPSIA

I R McFADYEN
M B Glasg
FLIGHT LIEUTENANT, R A F
From the Royal Air Force Hospital, Aden

A WOMAN, aged 19, had an eclamptic fit fifteen hours after she had her first baby She had given no evidence of pre-eclamptic toxæmia while pregnant, or during her eight-hour labour An episiotomy was necessary for delivery, and, in the course of its repair, she seemed drowsier than would have been expected from the 100 mg pethidine and the gas-and-air analgesia she had received during labour That night she slept uneasily, complaining of epigastric discomfort, and at 6 A M next day her blood-pressure (B P) was 140/90 mm Hg an hour later she had the fit

The patient was first seen during the sixteenth week of pregnancy No history of serious illness, previous pregnancy, or fits was given (this was confirmed in the puerperium) Her general condition was excellent Hæmoglobin 87% (Haldane), blood-group B, rhesus-positive, Kahn-negative The B P was 130/70, weight 105 lb , and her urine showed no abnormality Thirteen visits were made during the pregnancy Apart from a trace of albumin in a morning specimen of urine at the thirty-seventh week, and slight swelling of the ankles the week before that, the only abnormality of the pregnancy was a degree of hydramnios at the thirtieth week sufficient to warrant an X-ray of the abdomen The hydramnios decreased slowly but was still present at term The weight rose gradually to 128 lb at term, and fell 1 lb in the following week The blood-pressure remained between 110/60 and 120/80 during the pregnancy

Progress

Day 1 —A healthy 6½ lb infant, born ten days after the estimated delivery date The labour was uneventful Total blood loss 8 oz , 0 5 mg of ergometrine was given intramuscularly after delivery of the placenta

Day 2 —B P after the fit, 140/90 There was no residual paralysis, but facial œdema was noted and this increased during the next few hours The patient was sedated with barbiturates, and given a low-salt diet During the day her B P remained at about 130/90 Morphine was given that night as she complained of headache

Day 3 —The B P fell until it was 125/80 in the evening, the œdema subsided, and the patient had no complaints

Day 4 —About seventy-two hours after delivery the frontal headache and facial œdema returned The breasts became engorged and treatment for the suppression of lactation was begun Her temperature rose until it was 102 6°F by the evening She was moved into an air-conditioned room, and sedated with 6 g amylobarbitone six-hourly and 25 mg chlorpromazine orally twice daily The hæmoglobin was 88% (Haldane) and the hæmotocrit value 40%

Day 5 —A morning catheter specimen of urine contained 200 mg albumin per 100 ml , 15–25 red blood corpuscles, and 3–4 white corpuscles per high power-field, it was sterile A Foley catheter was introduced and nitrofurantoin 100 mg given six-hourly to prevent a urinary infection She passed 1290 ml of urine that day The œdema and headaches remained The temperature fell to 98 4° by the evening The blood-pressure, however, started to rise during the day

Day 6 —The B P continued to rise until in the evening it reached 170/100 At that point 12 5 mg hydrallazine was given orally this was followed an hour later by a fall in B P to 145/100 The dose was increased by stages to 37 5 mg four-hourly The B P fell gradually, until on the tenth day it was consistently 130/80 at the time that the next dose was due

The typical pre-eclamptic facies and headache remained until the sixth day when, along with the albuminuria, they started to subside On the ninth day the catheter was withdrawn, the administration of chlorpromazine was stopped, and the patient was moved out of the air-conditioned room The output of urine did not fall below 950 ml per twenty-four hours, nor did the blood-urea rise above 20 mg per 100 ml and the blood-electrolytes remained within normal limits

The hydrallazine was continued until the fifteenth puerperal day It was gradually reduced thereafter, and was stopped on the twentieth day The B P had then been 105/75 for three days, there was an occasional trace of albuminuria, and the patient had no symptoms The baby was bottle-fed and thriving

Six weeks after delivery the patient was seen at the postnatal clinic She had suffered no headaches or swelling of the ankles since leaving the hospital, nor were there any other complaints The urine contained no albumin, the B P was 110/75, and she weighed 106 lb Uterine involution was satisfactory

Discussion

Stander et al (1946) described 21 cases of eclampsia occurring within thirty hours of delivery 13 of these had shown no evidence of antepartum pre-eclamptic toxæmia In 9 cases of postpartum convulsions in the first twenty-four hours of the puerperium published by Hofmeister and Brown (1953), 2 had given no previous signs of pre-eclampsia Theobald (1955) quotes 4 cases of antenatal eclampsia in patients known to have been normal at some time in the twenty-four hours before the fits It is clear that this fulminating eclampsia can also occur in the puerperium It is not, however, common for a patient to develop the pre-eclamptic syndrome for the first time after delivery and after a fit, in none of these series is it mentioned Hamilton (1953) states that hypertension and convulsions may be produced by intravenous ergometrine given at the time of delivery, but this is not accompanied by œdema and albuminuria, and the blood-pressure usually settles within four hours

There is a school of thought which holds that pre-eclamptic toxæmia and eclampsia are due to increased myometrial tension, pointing out that twins and hydatidiform moles are examples of an overdistended uterus being frequently associated with pre-eclampsia Theobald (1955) gives as one of his essential criteria for any hypothesis purporting to explain the genesis of eclampsia that it must afford a reasonable explanation of eclampsia occurring up to four days after delivery of the placenta, and many find this a stumbling-block in accepting this hypothesis

A possible explanation of my case can be obtained from the concept of pregnancy as "a kind of physiological Cushing's syndrome" propounded by J S L Browne and elaborated by F J Browne (1958) In this it is held that the adrenal cortex undergoes hyperplasia in pregnancy under the influence of the large quantities of corticotrophin produced by the hypertrophied anterior pituitary and the placenta, and Poideven's (1959) demonstration of the relationship of striæ gravidarum to adrenal cortical hyperfunction supports it The excess of corticosteroids produced has been demonstrated by Gemzell (1953) who

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found that in the last three months of normal pregnancy the blood level of 17-hydroxycorticosteroids is four times the normal non-pregnant value. This would produce œdema and hypertension were it not that the healthy placenta inactivates the excess of pressor substance. If, however, placental function is diminished below some critical value by placental ischæmia (as may occur in essential hypertension, in a primigravid uterus which has hypoplastic vessels, or in twin pregnancy) pre-eclampsia develops. The same investigator has also shown that immediately after delivery the corticosteroid level is seven times the normal, but that it falls to the non-pregnant level by the sixth puerperal day. It might be expected that this would produce hypertension as the placenta is no longer present. This, in fact, happens. Browne (1958) quotes findings, in Sydney and London, that 20–30% of women whose blood-pressure remains within normal limits throughout pregnancy and labour are hypertensive in the first three days after delivery.

I have recently seen two patients in whom the pre-eclamptic syndrome developed after normal pregnancies; a third patient developed hypertension after a forceps delivery, during which she received two doses of 0·5 mg. ergometrine each.

Case 1.—A patient, whose first pregnancy and puerperium were quite uneventful, delivered her second child after a three and a half hour labour at term, and was given 0·5 mg. ergometrine intramuscularly. Antenatally her B.P. had not risen above 125/75, nor was there any other abnormality. One and a half hours after delivery she vomited and complained of headache. Her B.P. was then 180/110. She was sedated with morphine. Six hours later the headache was still present and she had developed generalised œdema with typical pre-eclamptic facies. The B.P. was 155/100, and a swab specimen of urine contained albumin ++. Sedation was continued and the œdema gradually settled. Thirty-six hours after delivery the headache and œdema had disappeared, the B.P. was 135/85, but there was still albuminuria. Thereafter the puerperium continued normally. The patient was discharged on the tenth puerperal day, her B.P. being 130/80, and the urine contained a trace of albumin.

Case 2.—Normal labour after a second uneventful pregnancy. A single intramuscular dose of ergometrine was given after delivery. On the third day of the puerperium the patient developed headache, hypertension (155/100) and gross generalised œdema. These increased in severity on the fourth day and then responded to rest in bed, sedation, and chlorothiazide therapy. She left hospital on the twelfth day, but the œdema recurred when she was at home and did not disappear for some weeks. The patient was a midwife, and remembered a similar sequence of events after her first confinement.

Case 3.—A primigravida with an uneventful antenatal course, the highest B.P. reading being 130/65. After a twenty-five hour labour she was delivered with forceps under pudendal block anæsthesia, because of second-stage delay. Ergometrine 0·5 mg. was given with delivery of the anterior shoulder. As the uterus tended to relax an intramuscular dose of 0·5 mg. ergometrine was given. One hour and fifty minutes after delivery she complained of nausea; the B.P. was then 170/105. The patient was sedated with amylobarbitone. The B.P. fell steadily; four hours after delivery it was 135/80, and it did not rise again. There was no œdema.

The development of the pre-eclamptic syndrome after emptying of the uterus in the first two of these cases could easily be interpreted in terms of the foregoing hypothesis. A similar transient hypertension to that occurring in the third case was noted after a cæsarean section where the patient also had a double dose of ergometrine, and it is probable that the rise in blood-pressure was caused by the ergometrine in both cases.

Summary

A case of postpartum pre-eclampsia with one eclamptic fit is described in a patient who had hydramnios but no pre-eclamptic toxæmia before delivery.

A possible explanation is that the already high blood-levels of 17-hydroxycorticosteroids during the last three months of pregnancy rise still more immediately after delivery, and do not fall to normal until the sixth puerperal day. Pre-eclampsia will occur in this period if, through ischæmia, placental function is reduced below some critical value. Postpartum pre-eclampsia may arise once the placenta is delivered, because the excess of pressor substance is then no longer inactivated, and hypertension and œdema result.

I wish to thank Dr. J. B. Hewitt for his encouragement in the preparation of this paper, and the Director General of Medical Services, Royal Air Force, for permission to publish.

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Preliminary Communication

HYALINE MEMBRANE FOLLOWING TOTAL BODY RADIATION

RELATION TO LUNG PLASMINOGEN ACTIVATOR

In 1940 Warren and Spencer[1] pointed out that hyaline membrane formation was the most definite of all changes produced in the lung by X-irradiation of the chest. These changes were observed after "chest wall doses" of 800–15,000 r. Though hyaline membrane was by no means pathognomonic of irradiation lung damage, its association with œdema, fibrosis, diminished inflammatory response, and hyalinisation of arterial walls was sufficiently unusual to enable irradiated lung to be distinguished from the non-irradiated. The pathogenesis of this lesion is not understood.[2]

Recently patients with far-advanced malignancies have been subjected to total body radiation (T.B.R.) at the National Naval Medical Center, utilising a dual ^{60}Co irradiator.[3] Clinical results are to be described elsewhere, but we wish to report that at necropsy hyaline membrane and fibrinoid deposits have been prominent in cases surviving at least two weeks after treatment.

Lieberman[4] has recently associated hyaline-membrane disease of children with deficiency of plasminogen activator in the lung. This tissue enzyme converts plasminogen to plasmin, the active fibrinolytic enzyme of the body. Lungs normally contain high levels of plasminogen activator.[4,5] Lieberman reasons that because of the relative insolubility of lung plasminogen activator its action is primarily local. In situations where there may be a pathological deposition of fibrin in the lungs, it would

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[1] Warren, S., Spencer, J. *Amer. J. Roentgenol.* 1940, 43, 682.
[2] Ellinger, F. Medical Radiation Biology, chapter 17. Springfield, Ill. 1957.
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[4] Lieberman, J. *New Engl. J. Med.* 1959, 260, 619; *Pediatrics*, 1960, 25, 417.
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LUNG ACTIVATOR ASSAY

Dose T.B.R.	Number of dogs	Days after radiation	Result
1000r	1 1 1	[illegible] 6 7	Positive Negative* Negative*
800r	1 1 1 1 1 1	[illegible] 8 9 10 11 12	Positive Negative Negative Negative* Negative Negative
700r	1	9	Positive
600r	1	9	Positive
Controls	10		Positive

* Assayed for inhibitor—all positive.

be the activator's function to activate the fibrinolytic system and effect the fibrin's removal. Persistence of fibrin deposits due to a defect in this system would lead to hyaline-membrane formation[4] and fibrosis.

The fibrin-plate technique of Astrup as outlined by Lieberman[4] was utilised and in addition fortified with 0·01 M Ca ions. The latter are added to saturate the citrate of commercial bovine fibrinogen and obviate non-enzymatic lysis of the fibrin.[5] This technique is considered quite sensitive and specific for the detection of plasminogen activator.[7]

OBSERVATIONS

Lieberman[4] has well documented the presence of activator in normal adult lung and this has been confirmed by us in a case of traumatic death. Two men who had undergone T.B.R. therapy were investigated. One had received 450r T.B.R. for disseminated lung cancer 18 days before death, and the other 1500r T.B.R. 15 days before death. The latter had no associated malignancy and had been treated in conjunction with an attempted transplant of kidney. In both instances hyaline membrane was present in the lung. Intensity of membrane formation has generally been associated with high dosage and survival for more than 6–8 weeks after therapy.[2] In both cases the assay of lung tissue failed to demonstrate any plasminogen activator.

To follow the sequence of events eleven dogs were subjected to T.B.R. in similar fashion to the human subjects. The table shows the results of assays of lung activator at various intervals in these eleven dogs and in ten controls.

The absence of activator in the irradiated animals could be due to inhibition. Portions of lungs from three animals with absence of activator were homogenised and the homogenate was mixed with equal volumes of an active lung homogenate. In each case the activity of the normal lung was completely inhibited. The animals tested are indicated in the table by an asterisk.

None of the lung sections showed the classical signs of radiation lung damage, and often they were described as normal. Since several weeks are generally required for the development of hyaline membrane,[2] and the animals in this dose range of T.B.R. seldom survive beyond the second week, this finding might be expected.

COMMENT

In two men treated by total body radiation hyaline membrane was found in the lung. Plasminogen activator was apparently absent.

The enzyme soon disappeared from the lungs of dogs given T.B.R. of 800–1000r, but these showed no morphologic change suggestive of the first stage of either hyaline membrane or fibrosis.

Our findings are consistent with the production in irradiated lung of a potent inhibitor of plasminogen activation.

Further studies are in progress to assess the influence of drugs and radiation technique on the activator system in the lung.

The opinions expressed in this paper are those of the authors and are not necessarily those of the Navy Department.

WILLIAM H. FLEMING
M.D. Georgia
Lieutenant, Medical Corps, U.S.N.R.
Head, Special Studies, U.S. Naval Hospital

JENO E. SZAKACS
M.D. Rome
Lieut.-Commander, U.S.N.
Pathologist, U.S. Naval Medical School

THOMAS C. HARTNEY
M.D. [illegible]
Lieutenant, Medical Corps, U.S.N.
Pathologist, U.S. Naval Medical School

National Naval Medical Center,
Bethesda, Maryland
U.S.A.

E. RICHARD KING
M.D. Ohio
Captain, Medical Corps, U.S.N.
Chief of Radiology, U.S. Naval Hospital

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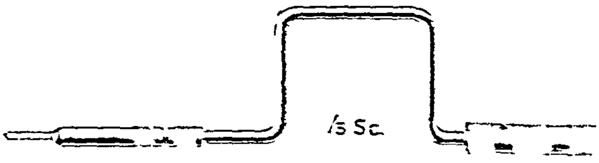
New Inventions

A BRACE SCREWDRIVER

ALTHOUGH Fitzgerald[1] described a brace screwdriver several years ago, this has never become popular, and the ease with which screws can be inserted by its use has not been generally appreciated.

Repeated gripping of a conventional screwdriver and pronating and supinating the forearm, can be very tiring—as many as 150 repetitions of this movement being necessary to insert four screws. The brace screwdriver, by its continuous action, removes this strain and also eliminates the inertia of the screw which develops each time we stop turning. The lessened resistance diminishes the chance of the screw breaking and the brace gives better control.



The type of brace is important. The model here illustrated, adapted from a socket spanner, can be held firmly along the axis of the screw. There should be no sleeve on the crank handle so that the hand can appreciate small changes in resistance during insertion. Some screw-holding attachment is essential. A simple holding sleeve, made by the London Splint Co. for one of their conventional screwdrivers, was used at first and proved quite satisfactory. The Williams screw-holding device, made by Chas. F. Thackray Ltd., although more elaborate, could also be used for this purpose. The brace here illustrated uses the Stryker screw-holding attachment. The Stryker attachment was devised for a power-driven continuously rotating screwdriver, and it is particularly suited to the rotary action of the brace. It has the great advantage over any other screw-holding attachments that the chuck not only releases the screw head automatically but also allows the screw to be fully driven home and tightened by one continuous action, thereby avoiding the need to complete the last few turns with a conventional screwdriver.

This final pattern of brace screwdriver is available from Messrs. Down Bros. Ltd., 21 St. Thomas Street, London S.E.1. By its use screws can be inserted into the upper femur with appreciably greater speed and precision than by any previously available hand-driven device.

Liverpool Royal Infirmary,
Liverpool 3

GEOFFREY OSBORNE
M.Ch. Orth. Lpool, F.R.C.S.

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Reviews of Books

The Problem of Acute Hypothermia

Editor P M STARKOV Translated from the Russian by R E HAMMOND Editor of English edition E NEIL, M D, professor of physiology, Middlesex Hospital Medical School London Pergamon Press 1960 Pp 329 70*s*

THIS book contains the results of many years research in Professor Starkov's department in Omsk There are twenty-eight articles by the fourteen workers concerned, and they are all physiological, though the hope is expressed that some of the conclusions may be put to practical use The subject titles alone make interesting reading, for, as might be expected, they imply a quite different approach to the physiology of hypothermia from that in the Western world, where much of the work has been planned pragmatically, according to the needs and problems of the operating-theatre, and not so much concern, perhaps, is felt about the basic differences between the body functions at normal temperature and those revealed during hypothermia Physiologists will therefore welcome the results of study on such fundamentals as cold effects on blood-flow in limbs and viscera, on the effects of direct cerebral cooling, and the use in hypothermia investigation of the values accorded by such familiar parameters as those of the heart-lung preparation, decerebrate cat, isolated rat uterus, and skeletal muscle Behaviour and conditioned reflexes in puppies and adult dogs are subjects of natural interest to Russian physiologists, and the response of these nervous patterns to hypothermia is the subject of one of Professor Starkov's own articles

The publishers regret that for speed and economy of production the text is in typescript photolithography, but the quality of the pages is even and good, and the content more than makes up for any deficiency The translation is commendably clear

Lectures on Hæmatology

Editor F J G HAYHOE, M D, M R C P, department of medicine, University of Cambridge London Cambridge University Press 1960 Pp 247 60*s*

THESE lectures were delivered at Cambridge in December, 1959, at a course for physicians and clinical pathologists "having hæmatology as one of their main interests" Four of these lectures will interest any hæmatologist J V Dacie gives some facts from his unique experience in hæmolytic anæmia, W M Davidson provides an excellent account of iron metabolism and treatment, G Wetherley-Mein describes interestingly and practically what is meant by "myeloproliferative syndromes", and R M Hardisty makes a gallant attempt to bring together in a moderately coherent account what we now know about hæmostatic processes The other lectures are good, sometimes very good, reporting work that will be familiar to many hæmatologists R H Girdwood on megaloblastic anæmias, George Discombe on transfusion hazards, and J C White on hæmoglobin variants summarise their already published work Dr Hayhoe himself draws on some pages from his recent book on leukæmia Richard Doll writes on the incidence of leukæmia and the significance of environmental factors, D A G Galton on the chemotherapy of leukæmia, G I C Ingram on congenital and acquired disorders of blood coagulation, and J F Ackroyd on the pathogenesis of purpura H E M Kay brings together a useful summary of published results on attempts to use marrow transplants in the treatment of leukæmia

This sort of book falls between two stools the specialist in hæmatology will be interested only in the first four lectures we mentioned, the more general physician or pathologist with a main interest in hæmatology will hardly wish to buy a set of lectures that will need revision in a short time, especially when he can buy a whole textbook of hæmatology, containing nearly everything in this volume and a lot more, for rather less This volume is to be one of a series why not publish the others in a less expensive form—say, paper back with plastic binding and without some of the illustrations, none of which, in this hæmatology volume, are really necessary?

Chemical Micromethods in Clinical Medicine

R H WILKINSON, M D, assistant chemical pathologist, The Hospital for Sick Children, London Oxford Blackwell Scientific Publications 1960 Pp 121 40*s*

EMPHASIS on micromethods in chemical pathology has increased steadily during the past twenty years It was gradually realised that blood-sugar and blood-urea were not the only substances that could be measured using capillary blood and that it was obviously more considerate and convenient to take small samples of capillary blood by needle-prick than larger ones from a vein by syringe It has also become clear that small amounts of heparinised blood may yield as much plasma as larger amounts of clotted blood can yield serum These considerations apply particularly to pædiatrics, and in this country notable contributions to microchemical methods have come from The Hospital for Sick Children, Great Ormond Street, and some very important ones from the author of this little book There are only about 100 pages of text, of which 10 are taken up by illustrations, not all of them essential (a page is used for a photograph of a Van Slyke manometer and another for its micro version, and almost a whole page is given to a photograph of the EEL flame photometer, which has been in routine use in virtually all pathology laboratories for many years) Most of the methods for examining blood in a pædiatric hospital are clearly described (the estimation of serum-iron is not among them) Micromethods only are considered, and this excludes many important pædiatric investigations of urine and fæces

Principles of Animal Virology (2nd ed New York and London Academic Press 1960 Pp 490 86*s*)—This book, edited by Sir Macfarlane Burnet, O M, F R S, is very different from Burnet and Stanley's *The Viruses*,[1] and is much more concerned with viruses of men and animals as agents of disease A particularly interesting aspect is its emphasis on the ecology of viruses and on evolutionary aspects of virus development Much of the book is written from a very personal viewpoint, and the references are selective rather than comprehensive Nearly half the text of the first edition, which appeared five years ago, has been rewritten

Preventive Medicine and Public Health (4th ed London H K Lewis 1960 Pp 316 27*s* 6*d*)—It is no easy matter in these days to write a universally acceptable student textbook on public health, there is still so much diversity of opinion about the legitimate scope of the subject and so much variation from school to school in attention given to it Prof Fred Grundy's book aims to be an introduction for students and practitioners and it obviously meets a want, for it is now in its fourth edition in ten years The book is necessarily simple in its approach, and some of its pictures could perhaps be shed without much loss, but it does provide an outline of basic principles and for the zealous it offers suggestions for further reading

Hypnoanalysis (New York Grove Press London John Calder 1960 Pp 342 16*s* 6*d*)—Dr Lewis R Wolberg's wide experience of hypnosis is well known, and some of his writings have become classics This paperback, which is a reprint of a 1945 Grune & Stratton edition, is devoted to the use of hypnotic techniques during psychoanalysis, in this case Freudian The first 136 pages describe the treatment of one patient, then follows a 21-page "dynamic formulation" by Dr A Kardiner, and in the final 179 pages Dr Wolberg suggests the various ways in which hypnosis can be of use in psychoanalytic treatment The case-report is certainly of great interest, notwithstanding the doubt in diagnosis, and Dr Wolberg writes better than most analysts, but the work will do little to convince the sceptical Practitioners who use either of these techniques will find the book interesting, but there must be serious reservations about presenting this new edition to the large lay readership for which it is presumably intended

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[1] See *Lancet*, 1959 ii, 548 *ibid* Oct. 29, 1960, p 961

THE LANCET

LONDON 5 NOVEMBER 1960

Coming Home and Going Abroad

ON achieving independence, a Colony naturally wants to have all its services manned by its own people, and that is something to which every new nation should look forward. But commonly the wellbeing and progress of Colonies have depended largely on the devoted work of administrative and professional officers from overseas, and usually these ought to go on with that work until there are enough properly qualified indigenous officers to replace them. Unfortunately the insecurity of a new regime may lead to an exodus of many of the men and women whom the new country will most need in the next few years. The anxieties of a Civil Servant in a country likely to become self-governing are well depicted in the white-paper[1] issued last week:

> “ the sense of vocation which led him into the Public Service in an overseas territory still remains, but he is beset by uncertainty as to the extent to which he will be able to fulfil it under the new conditions. his status in public affairs is changing and very often he and perhaps his family also are subject to discomforts stemming naturally from a period of rapid political change, and until reassurance is given him on the shape of his future he must live through a period of extreme doubt about the years ahead.”

To prevent the “tragic waste of human skills and wisdom” inevitable where a service runs down through departure of its key members, the British Government, as announced last July,[2] are offering ten-year agreements to most Colonial territories by which the territory need pay little more to employ someone from overseas than to employ one of its own nationals.[3] In respect of some 21,000 officers of the Overseas Civil Service (appointed by the Colonial Office or the Crown Agents) the Government will be responsible (1) for the expatriation or inducement element often added to basic salaries to attract overseas candidates, (2) for the corresponding part of the pension, (3) for education and children's allowances, (4) for half the cost of leave passages, and (5) for half the cost of compensation payable for premature retirement. While this excellent scheme can be looked on as an act of justice towards people who have been encouraged to take overseas appointments under the Crown, it is also much more. It is an important offer of assistance, during the transition period, to territories which may see the advantages of retaining expatriate officers but might otherwise be unable to keep them. The cost to Britain is estimated at between £12 million and £16 million a year.

Two years ago at the British Medical Association's conference on overseas appointments,[4] one speaker said bluntly that if men are expected to go and work in the Colonial Service, arrangements must be made for them when they come back. An attractive suggestion which is firmly turned down in an appendix to the white-paper is that the Civil Services at home and abroad should be unified, so that members could expect a full career, if not in the Colonies then at home. But in point of fact the home Civil Service, with an administrative staff of less than 2500, can offer comparatively few openings to men returning from abroad, and the vacancies now likely to be offered to such men by other Colonies will usually be in a basic grade, and for only one or two tours of service. The creation of a unified service based on the United Kingdom would, it is felt, give a false impression, because it could create no jobs for which members of the Overseas Civil Service are not already eligible. Though some of these will enter the home Civil Service, or the Foreign Service, or may be assigned to other countries under technical-assistance agreements or similar arrangements, they cannot be sure of such employment, and for this reason the Colonial Office in July, 1957, set up an Overseas Services Resettlement Bureau to find them, if need be, alternative posts. Of 1710 applicants the bureau has so far found employment for over 1000—about 500 of them in the past year. The Government hope that “the knowledge that the Bureau will be there to assist them when required will both encourage officers to continue their overseas service, and new recruits to join it.”

To the returning doctor even less than to the administrator can the Government guarantee a post at home, and latterly the difficulty of getting one has been a misfortune both to those who applied and to the public which has often been denied their services. The Government's own medical establishment is small and specialised, and the Ministry of Health, even when it accepts a moral obligation to get a particular specialist appointed or reappointed to the National Health Service, finds regional hospital boards properly reluctant to choose anyone other than the best applicant for the job. If the specialist has difficulty in establishing himself in this country, the difficulty can be even greater for general-duty officers who, though they may have been doing general practice at a high level, have usually been unable to secure National Health Service practices against the competition of younger men who have stayed here. The gloom over our failure to reabsorb so many of our able people who have had the courage and enterprise to work abroad was epitomised in the statement of a speaker, two years ago, that he could not see how general-duty medical officers returning from Colonial service can fit in anywhere at any level in our medical services. And this gloom seems as inspissated as ever, causing even the most sanguine to speak of this problem of medical resettlement as largely insoluble. But are we not in fact dealing with a hangover rather than an incurable illness? If, as LAFITTE and SQUIRE[5] say, this country is shortly going to wake up and find

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[1] Service with Overseas Governments. Cmnd 1193. H.M. Stationery Office. Pp 22. 1s. 3*d*.

[2] *Hansard*, July 28, 1960, col. 1869.

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[4] See *Lancet*, 1958, ii, 1111.

[5] Lafitte, F., Squire, J. R. *ibid*. Sept. 3, 1960, p. 538.

Reviews of Books

The Problem of Acute Hypothermia

Editor P M Starkov Translated from the Russian by R E Hammond Editor of English edition E Neil, M D, professor of physiology, Middlesex Hospital Medical School London Pergamon Press 1960 Pp 329 70*s*

This book contains the results of many years research in Professor Starkov's department in Omsk There are twenty-eight articles by the fourteen workers concerned, and they are all physiological, though the hope is expressed that some of the conclusions may be put to practical use The subject titles alone make interesting reading, for, as might be expected, they imply a quite different approach to the physiology of hypothermia from that in the Western world, where much of the work has been planned pragmatically, according to the needs and problems of the operating-theatre, and not so much concern, perhaps, is felt about the basic differences between the body functions at normal temperature and those revealed during hypothermia Physiologists will therefore welcome the results of study on such fundamentals as cold effects on blood-flow in limbs and viscera, on the effects of direct cerebral cooling, and the use in hypothermia investigation of the values accorded by such familiar parameters as those of the heart-lung preparation, decerebrate cat, isolated rat uterus, and skeletal muscle Behaviour and conditioned reflexes in puppies and adult dogs are subjects of natural interest to Russian physiologists, and the response of these nervous patterns to hypothermia is the subject of one of Professor Starkov's own articles

The publishers regret that for speed and economy of production the text is in typescript photolithography, but the quality of the pages is even and good, and the content more than makes up for any deficiency The translation is commendably clear

Lectures on Hæmatology

Editor F J G Hayhoe, M D, M R C P, department of medicine, University of Cambridge London Cambridge University Press 1960 Pp 247 60*s*

These lectures were delivered at Cambridge in December, 1959, at a course for physicians and clinical pathologists "having hæmatology as one of their main interests" Four of these lectures will interest any hæmatologist J V Dacie gives some facts from his unique experience in hæmolytic anæmia, W M Davidson provides an excellent account of iron metabolism and treatment, G Wetherley-Mein describes interestingly and practically what is meant by "myeloproliferative syndromes", and R M Hardisty makes a gallant attempt to bring together in a moderately coherent account what we now know about hæmostatic processes The other lectures are good, sometimes very good, reporting work that will be familiar to many hæmatologists R H Girdwood on megaloblastic anæmias, George Discombe on transfusion hazards, and J C White on hæmoglobin variants summarise their already published work Dr Hayhoe himself draws on some pages from his recent book on leukæmia Richard Doll writes on the incidence of leukæmia and the significance of environmental factors, D A G Galton on the chemotherapy of leukæmia, G I C Ingram on congenital and acquired disorders of blood coagulation, and J F Ackroyd on the pathogenesis of purpura H E M Kay brings together a useful summary of published results on attempts to use marrow transplants in the treatment of leukæmia

This sort of book falls between two stools the specialist in hæmatology will be interested only in the first four lectures we mentioned, the more general physician or pathologist with a main interest in hæmatology will hardly wish to buy a set of lectures that will need revision in a short time, especially when he can buy a whole textbook of hæmatology, containing nearly everything in this volume and a lot more, for rather less This volume is to be one of a series why not publish the others in a less expensive form—say, paper back with plastic binding and without some of the illustrations, none of which, in this hæmatology volume, are really necessary ?

Chemical Micromethods in Clinical Medicine

R H Wilkinson, M D, assistant chemical pathologist, The Hospital for Sick Children, London Oxford Blackwell Scientific Publications 1960 Pp 121 40*s*

Emphasis on micromethods in chemical pathology has increased steadily during the past twenty years It was gradually realised that blood-sugar and blood-urea were not the only substances that could be measured using capillary blood and that it was obviously more considerate and convenient to take small samples of capillary blood by needle-prick than larger ones from a vein by syringe It has also become clear that small amounts of heparinised blood may yield as much plasma as larger amounts of clotted blood can yield serum These considerations apply particularly to pædiatrics, and in this country notable contributions to microchemical methods have come from The Hospital for Sick Children, Great Ormond Street, and some very important ones from the author of this little book There are only about 100 pages of text, of which 10 are taken up by illustrations, not all of them essential (a page is used for a photograph of a Van Slyke manometer and another for its micro version, and almost a whole page is given to a photograph of the EEL flame photometer, which has been in routine use in virtually all pathology laboratories for many years) Most of the methods for examining blood in a pædiatric hospital are clearly described (the estimation of serum-iron is not among them) Micromethods only are considered, and this excludes many important pædiatric investigations of urine and fæces

Principles of Animal Virology (2nd ed New York and London Academic Press 1960 Pp 490 86*s*)—This book, edited by Sir Macfarlane Burnet, O M, F R S, is very different from Burnet and Stanley's *The Viruses*,[1] and is much more concerned with viruses of men and animals as agents of disease A particularly interesting aspect is its emphasis on the ecology of viruses and on evolutionary aspects of virus development Much of the book is written from a very personal viewpoint, and the references are selective rather than comprehensive Nearly half the text of the first edition, which appeared five years ago, has been rewritten

Preventive Medicine and Public Health (4th ed London H K Lewis 1960 Pp 316 27*s* 6*d*)—It is no easy matter in these days to write a universally acceptable student textbook on public health, there is still so much diversity of opinion about the legitimate scope of the subject and so much variation from school to school in attention given to it Prof Fred Grundy's book aims to be an introduction for students and practitioners and it obviously meets a want, for it is now in its fourth edition in ten years The book is necessarily simple in its approach, and some of its pictures could perhaps be shed without much loss, but it does provide an outline of basic principles and for the zealous it offers suggestions for further reading

Hypnoanalysis (New York Grove Press London John Calder 1960 Pp 342 16*s* 6*d*)—Dr Lewis R Wolberg's wide experience of hypnosis is well known, and some of his writings have become classics This paperback, which is a reprint of a 1945 Grune & Stratton edition, is devoted to the use of hypnotic techniques during psychoanalysis, in this case Freudian The first 136 pages describe the treatment of one patient, then follows a 21-page "dynamic formulation" by Dr A Kardiner, and in the final 179 pages Dr Wolberg suggests the various ways in which hypnosis can be of use in psychoanalytic treatment The case-report is certainly of great interest, notwithstanding the doubt in diagnosis, and Dr Wolberg writes better than most analysts, but the work will do little to convince the sceptical Practitioners who use either of these techniques will find the book interesting, but there must be serious reservations about presenting this new edition to the large lay readership for which it is presumably intended

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[4] See *Lancet* 1958 ii 1111

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Similarly the apparent risks of going abroad for a few years, on secondment or otherwise, may begin to bulk less large in the minds of candidates The Government are in favour of secondment from their own services here, and propose to have talks with representative bodies of employers " to seek their agreement to releasing staff on loan "—paying " in appropriate cases the differential between the terms of the overseas appointment and the local salary " If there are still senior members of the profession who are inclined to discourage their juniors from going abroad, we hope they will give thought to the white-paper's correct statement that service overseas affords " opportunities to do interesting work in a new environment, opportunities to exercise individual initiative and responsibility at an earlier age than is usual here, opportunities to develop personal qualities of self-reliance, leadership and adaptability arising from the wide variety of tasks to be undertaken opportunities to make an individual contribution to the development of a new country " Even more, perhaps, we hope they will read the remarkable review of the African situation, by Dr H S GEAR, which we publish this week Though GEAR credits colonialism with having given Africa a phase of social stability with a rising economy, and recognises that the main medical contribution has been, and still is, made by the official services, he is concerned mainly with the unofficial aspects of a system which hitherto has been continually nourished and refreshed from Europe " Medicine's true teachers and disciples give more to Africa," he says, " than medical care in a hospital or clinic ", and Western medicine should not overlook the need for this broader interpretation of its possible service " It should guide Africa to create people who are good doctors and nurses, but are also prepared to follow fearlessly the principles founded over many difficult generations in Europe and America "

Protein in Hyaline Membrane

THE chief component of the hyaline membrane found on histological examination of the lungs of premature infants who have died shortly after birth was once believed to be inspissated material derived from the amniotic fluid or vernix caseosa, and the term " vernix membrane " was used for some years [1] It now seems that a fundamental disorder of the pulmonary circulation plays a part in the formation of the membrane,[2] protein being extravasated from the pulmonary vessels into the neighbouring air-spaces and then forced by inspiration *into a membrane lining the walls of these spaces*

While most agree that the bulk of the membrane is composed of protein, there is still some difference of opinion as to its origin and nature LYNCH [3,4] initially suggested that the membrane represented a dried and concentrated secretion of the respiratory bronchioles and alveolar ducts Further work indicated that the membrane included hæmoglobin,[5] but the bulk of it was composed of fibrin [6,7] All these investigations reinforced the idea that the components of the membrane were derived from the blood-stream The various cardiovascular factors associated with hyaline-membrane formation were analysed by SHANKLIN [8] in a series of 335 premature infants He found that membrane formation was significantly more frequent in association with cardiac malformation that increased the pulmonary blood-flow The stages of the development of the pulmonary lesion were thought to be increased pulmonary blood-flow, left ventricular failure, pulmonary œdema, and membrane formation The possibility that maternal factors may play a part in the presumed circulatory disturbance has been investigated by COHEN et al ,[9] whose work seems to indicate that membrane formation is commoner when the pregnancy has been complicated by toxæmia and especially by antepartum hæmorrhage From time to time it has been claimed that the frequency of hyaline membrane is increased in infants delivered by cæsarean section [10], but COHEN et al conclude that any such increase is limited to pregnancies where bleeding has occurred before delivery

The composition of hyaline membrane has been investigated by BUCKINGHAM and SOMMERS [11] They regard the structure as laminated acellular layers of eosinophilic material apposed to the walls of alveolar ducts, alveoli, and terminal bronchioles Ultraviolet microscopy showed that the material closely resembled plasma-protein or cell cytoplasm, in addition, some nucleoprotein was thought to be present Membranes produced experimentally by exposure of mice to oxygen had a similar composition The membranes thus seemed to comprise cytoplasmic material, hæmoglobin, polymerised fibrin, nucleoprotein, and mucoprotein These workers were impressed by degenerative changes in the bronchiolar epithelium, which they believe contribute to membrane formation Hyaline membrane may possibly be associated with hypersecretion of alveolar lining substance [12] which raises the question whether abnormal autonomic nervous stimulation enhances its formation, not only by promoting pulmonary œdema but also by increasing secretory activity in the terminal air-passages

Although highly specialised techniques have revealed fibrin in hyaline membrane, this does not stain for fibrin by ordinary histochemical methods It has been shown, however, that a hyaline material is formed when certain acid mucopolysaccharides react with plasma-proteins [13,14], and the possibility that a similar mechanism may operate in hyaline-membrane formation has been investigated by CARONE and SPECTOR,[15] who induced pulmonary œdema in rats by means of α-naphthyl thiourea and then introduced, by the endotracheal route, various substances including dextran sulphate, nasal mucus, meconium, and concentrated amniotic-fluid suspension All these substances contain acid mucopolysaccharides, and all produced a membrane which had similar tinctorial properties to those of the membrane found in the human lung and which also failed to stain for fibrin This suggests that, if hyaline membrane is indeed largely composed of fibrin, then this is probably in a polymerised form Similar membranes were also produced when these acid mucopolysaccharides were introduced via the trachea together with plasma-protein in animals not previously given α-naphthyl thiourea

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[1] Farber S , Wilson J L *Arch Path* 1932, 14, 437
[2] See *Lancet*, 1958 ii, 945
[3] Lynch, M J G , Mellor, L D *J Pediat* 1955, 47, 275
[4] Lynch M J G Mellor, L D *ibid* 1956, 48, 165
[5] Lynch, M J G , Mellor L D , Badgery, A R *ibid* p 602
[6] Gitlin D , Craig J M *Pediatrics* 1956, 17 64
[7] Van Breemen V L , Neustein, H B , Bruns, P D *Amer J Path* 1957, 33, 769
[8] Shanklin D R *Arch Path* 1959, 68 49
[9] Cohen M M , Weintraub, D H , Lilienfeld, A M *Pediatrics*, 1960, 26, 42
[10] See *Lancet*, 1960 i, 686
[11] Buckingham, S , Sommers, S C *Amer J Dis Child* 1960, 99, 216
[12] Pattle, R E *Proc roy Soc B* 1958, 148, 217
[13] Walton, K W *Brit J Pharmacol* 1954, 9, 1
[14] Pappas G D Ross M H , Thomas L *J exp Med* 1958, 107, 333
[15] Carone, F A , Spector, W G *J Path Bact* 1960, 80, 63

Even if the membrane is largely composed of fibrin, the reason for the chain of events leading up to fibrin precipitation in the lungs of some infants but not of others still has to be found A possible clue is afforded by the work of LIEBERMAN[16] As a result of preliminary studies he postulated that a deficiency of lung plasminogen-activator activity predisposed certain infants to hyaline-membrane formation. It could be objected that such a low enzyme activity might result from exhaustion of supply by the disease process itself[17], but any such doubt has been largely settled by LIEBERMAN and KELLOGG,[18] who have now evolved an improved technique for measuring tissue plasminogen-activator activity They describe their findings in specimens obtained from 61 fœtuses and newborn infants, comprising 15 cases of hyaline membrane and 46 controls All but 2 (4%) of the control series showed plasminogen-activator activity, and none showed any inhibitor activity By contrast none of the 15 membrane cases showed activity when lung cubes were examined, but in 2 out of 11 cases homogenised tissue showed some activity The remaining 9 cases studied by tissue homogenisation showed no activator activity, and in 8 of them evidence of inhibitor activity was found These results confirm the previous observation of defective plasminogen-activator activity in association with hyaline membrane The inhibitor of the enzyme, found in most of the affected lungs, may explain the lack of success which has attended the therapeutic use of fibrinolytic agents in affected babies In a preliminary communication in our present issue Dr FLEMING and his associates at the National Naval Medical Center at Bethesda report apparent absence of plasminogen activator in the lungs of two men whose hyaline membrane followed "total body irradiation", and their findings in dogs were consistent with the view that irradiation produces a potent inhibitor of activation LIEBERMAN and KELLOGG suggest that, in infants, the enzyme defect may be genetically determined

SETNIKAR et al[19] suggested that an alveolar transudate is an essential part of amniotic fluid. If this is so, a rich source of fibrin is contained in the fœtal lung, and, if fibrinolytic activity is defective or absent, fibrin deposits may gradually accumulate and form into membranes after the onset of respiration Again, deficient proteolytic activity in the lung may interfere with the alveolar lining layer and so affect the surface tension in the pulmonary air-spaces Such an increase in the surface-tension is thought to promote atelectasis[20]

Although much work is being done on hyaline membrane, it is abundantly clear that our understanding of its formation is still deficient, and no effective remedy is in sight

Troubled Families

> " the State's principal duty is to assist the family in carrying out its proper functions "

So say the Ingleby Committee whose report,[21] published last week, gives important and far-reaching advice on means of helping delinquent, disturbed, and neglected children under 17 Unfortunately cause and prevention did not enter into their terms of reference, but it is clear that the committee believed that the family and the relationships therein were the primary causes of later difficulties, whatever secondary influences may subsequently play a part—an emphasis which colours the recommendations throughout The parents, as much as the disturbed child, need to alter their ways, and the committee have wisely regarded the child as a person to do things *round* rather than the patient or sinner to do things *to*

Set up by the Home Secretary in 1956, the committee[22] record that at that time falling delinquency-rates and fewer maintenance and affiliation orders set a scene which, if not rosy, was at least hopeful But since then this trend has been dramatically reversed, so that the Ingleby recommendations gain much in significance and will be given prompt Governmental scrutiny

Considering first the ways in which help reaches the family, the report notes that inter-service rivalry has, in the past, impaired coordination and delayed the arrival of appropriately trained workers Thus, while the committee welcome the help of almost any agency in bringing troubled families and children to notice, diagnosis and treatment require tactful handling and, very often, special skills not always found among those who concern themselves with the personal affairs of others A reorganisation of the various family services is called for, with the establishment of an independent "family bureau" responsible only to the clerk to the local authority Detailed consideration of local-government changes was beyond the committee's terms of reference and they urge further study of this matter, bearing in mind that differing local circumstances will call for flexibility in legislation designed to ensure efficient coordination The report declares that " there should be a general duty laid upon local authorities to prevent or forestall the suffering of children through neglect in their homes," and such authorities should be required to submit schemes for Ministerial approval The only bodies, the report goes on, with the power to bring a case before the courts should be the police and the local authority—a move, it seems, away from the sometimes harmful multiplicity of authorities bearing on the family This proposal, which removes such power from the National Society for the Prevention of Cruelty to Children, is likely to be a contentious one when debated in Parliament and elsewhere, but it is in tune with the legitimate trend towards professionalism in social work The days of the keen but untutored amateur are passing, and rightly so The reluctance of the committee to widen " juvenile liaison schemes ", run by the police for cautioned offenders, springs from similar judgment

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[16] Lieberman J *New Engl J Med* 1959, 260, 619
[17] See *Lancet*, 1959 i 1234
[18] Lieberman J, Kellogg, F *New Engl J Med* 1960 262, 999
[19] Setnikar L, Agostoni E., Taglietti A. *Proc Soc exp Biol, N Y* 1959, 101, 842
[20] Avery, M. E. Mead J *Amer J Dis Child* 1959, 97 517
[21] Report of the Committee on Children and Young Persons Cmnd. 1191 H.M Stationery Office. Pp 179 8s
[22] The members were Lord INGLEBY (chairman), Lady ADRIAN, Hon. Mrs P L AITKEN, Mr R. H BLUNDELL, Mr DONALD FORD, Dr R. M. JACKSON, Mrs M. M C KEMBALL, Mr G H. MCCONNELL, Prof ALAN MONCRIEFF, Viscountess RIDLEY, Dr P D SCOTT, Mr G A. WHEATLEY, Alderman D T WILLIAMS, and Mr J P WILSON

Turning to jurisdiction, the committee note the trend, over the past century or so, towards separate provision under the criminal law for the young and, more and more, towards emphasis on the welfare of the child as the overriding concern This has led, the committee believe, to inconsistencies The principle of criminal responsibility and punishment for a certain act in a judicial setting has become uncertainly combined, by statute, with the obligation to serve the child's best and broadest interests Thus a trivial offence may, when the full appalling family circumstances become known to the court, lead to a seemingly severe and drastic disposal Furthermore, the widening of the court's function in 1908 and 1933 permitted a child to be sent to an approved school (a severe punishment very often) for the non-criminal offences of being " beyond control " or in need of " care or protection " In rethinking the place of juvenile courts the committee concluded cautiously that, however much a child may seem likely to benefit from interference by the State, compulsory intervention should not be applied except for the clearly defined and well-known reasons that already obtain The basic pattern of courts, too, with lay justices still finds favour with they committee, though they concede some virtues to the non-judicial tribunal

The trend away from criminal jurisdiction, however, should be urged forward, notably by raising the minimum age of criminal responsibility from 8 to 12 years, and later perhaps to 13 and 14 Though an important change of principle, the practice of the law would not be as much affected by this as might be imagined Already offending children under 8 may be brought before a court and dealt with as " beyond control " the court, under these proposals, will certainly not allow children to " get off ", indeed by the greater thoroughness of the procedure, Society may expect better protection than before Children under 12 would no longer be charged with an offence, though if such were established (under the usual rules of evidence) it would count towards showing that the child was " in need of protection or discipline "—the new form of words empowering the court to take action The procedure would be swifter (cases would have to be tried within 28 days of detection, save in special circumstances) and more holistic, taking in the whole circumstances of the case The police and local authority would consult before proceedings began Though retaining the power to remove a child from home, the court would do so only when it was satisfied that his needs could not be somehow met without such action, and it would have the additional options of ordering attendance at an attendance centre or study in a remand home Fines and detention in detention centres would be withdrawn, but compensation to a maximum of £100 and/or costs could be demanded Committal to the care of a " fit person " would remain, and parent or guardian could be ordered to enter recognisance to exercise proper care and guardianship The court could also order supervision by a probation officer or other person for up to 3 years From 12 to 17 years procedure would be much as it is now, and the committee did not feel that the age-limit of 17 for juvenile courts should be raised, though they wondered whether a sort of half-way " youth court " for ages 17 to 20 or 21 might be examined further

The committee believe that the court needs to be much more active with the parents, summoning the attendance of both, bringing home to them their share of responsibility, and offering support where it is practicable The verdict of the court—so often a source of grievance—would be explained to them as far as possible Treatment, where compulsory, appears as punishment, and the committee admit that in practice it is impossible to distinguish between them On the other hand, parents would no longer have the right to bring children before the court as " beyond control ", though appeal to the local authority might sometimes have the same effect if no other solution could be found Here, however, parents would not appear in the role of prosecutor, and the need for them to make damaging and rejecting statements towards the child in public would be reduced

The greater part (some 400 out of 550 paragraphs) of the report is a review of administrative detail arising partly from this survey and related to courts, sentences, and corrective institutions Few of the numerous recommendations will be disputed, nor are many of wide interest, important though they are Thus, an adequate course of training is recommended for all juvenile-court magistrates, who should usually be lay people, appointed between about 30 and 40 and retiring at 65 Better court-room accommodation for the children is needed, and the report calls for removal of all legal obstacles to accelerate the disposal of cases involving child witnesses, plus closer liaison with adult courts where necessary The committee approved the attendance-centre principle sufficiently to want to lower the minimum age to 10 and to widen the categories of offenders treated there For detention centres, however, a uniform 3-month sentence should take the place of the present sliding scale between 1 month and 6 (for under 17s only), and the committee are surely right in pressing for compulsory aftercare for a further 6 or 12 months

Approved schools are left much as they are, with a few hopeful calls for inter-school staff discussions and better psychiatric facilities, staff, and aftercare Recent months have made it clear that all is far from well among the approved schools, but from present knowledge it is hard to see how the committee could go further than they have, timid though their recommendations seem Finally, the committee want to extend somewhat the prosecution of cruel parents (to take in mental suffering short of actual derangement) and to increase the penalties to £100 or 6 months' imprisonment or both, though at the same time full use should be made of residential training and social aid

In sum, these proposals do not seem to conflict with any of the many other Governmental reflections of recent years, and they all have it in common that the big problem in realising them is shortage of staff and money (We have now heard from so many committees that a "survey of reports" might help to place the future of our social services in comprehensive perspective) There is little of dynamite in the Ingleby recommendations Juvenile-court organisation, in particular, has been left largely alone, to the disappointment, undoubtedly, of many But the committee have reached a quite surprising degree of unanimity after their 4-year pilgrimage, and few who advocate sweeping changes have given such careful thought to the implications These proposals, in the present state of therapeutic knowledge, are probably as far as we should go and must carry an excellent chance of early Parliamentary acceptance Coming when voluntary acceptance of child and family guidance services is spreading and when compulsory treatment for "psychopaths" is becoming possible under the National Health Service we have now the foundations of an excellent service for children The wisdom of this report cannot be in doubt, and the sooner it all happens, the better it will be for everyone

Annotations

SOCRATES IN HARLEY STREET

SOME two years ago, in a week when medical education was being considered at a formal conference in London, we printed a less orthodox discussion of the same problems in our peripatetic columns It began

> ALCIBIADES Tell me, Socrates, how can we be sure that our doctors are well trained?
>
> SOCRATES Do you think it right, Alcibiades, that we should say of a pudding that it is good or bad?
>
> ALCIBIADES Certainly, Socrates
>
> SOCRATES It must be possible then to distinguish a good pudding from a bad one?

This learned ballon d'essai pleased readers, author and editor Socrates was offered a column of his own, and throughout 1959 under the heading of "Dialogues of Today" he and his disciples debated in our columns some of the social and moral uncertainties of medicine and humanity, of our time and all times Because the dialogues deal with problems which belong not only to medicine and not only to this country, we have reprinted them as a small book (with paper covers)[1] for the consideration of all who enjoy a good argument

The dialogues range from birth control to death control, from ways of constituting a committee to the reasons for constituting a college, from the atomic bomb to less final methods of retirement But if the matter is serious the manner is never heavy No dogmatic conclusions are offered and the reader is left to continue the debate with his own friends—and perhaps with himself The anonymous author admits that he has chosen the conversational form with provocative intent His introductory quotation, borrowed from David Hume, another writer of dialogues, describes dialogue writing as peculiarly suitable for a topic which is obvious but important or for one which is so obscure and uncertain that the human reason can reach no fixed determination with regard to it "Reasonable men," Hume adds, "may be allowed to differ, where no one can reasonably be positive Opposite sentiments, even without any decision, afford an agreeable amusement" We hope that all our reasonable readers will find agreeable amusement with Socrates

CHOLESTATIC VIRAL HEPATITIS

EVEN before the 1939–45 war it was recognised that a varying but small proportion of cases of epidemic viral hepatitis differed from typical cases in the difficulty with which they could be distinguished from cases of extrahepatic biliary obstruction[1] Histologically the liver in such cases was characterised by the extreme mildness of the parenchymal lesions and their restricted focal distribution, the conspicuous features were multiple intralobular plugs of bile and moderate to severe infiltration of the portal tracts with both mononuclear cells and polymorphs Hitherto deviation from the more usual pattern of the disease has not been satisfactorily explained

Dubin et al,[2] on the basis of their experience at a U S Army Hospital in the years 1951–53, suggest that the cholestatic form of hepatitis may be due to a variant of the usual virus Their clinical material comprised 93 cases of viral hepatitis in which biopsy of the liver was undertaken within twenty-one days of the onset of jaundice By means of clearly defined criteria these cases were classified into four types Type A showed the diffuse necrosis with very slight bile stasis that is typical of classical viral hepatitis Type B was similar, but intralobular plugs of bile indicated some added cholestasis Type C was characterised by focal distribution of the parenchymal lesions and predominance of cholestasis In type D parenchymal necrosis was negligible, the changes consisting almost entirely in bile stasis and cellular infiltration of the portal tracts Patients with lesions of types A or B were regarded as having classical viral hepatitis, and those with lesions of types C or D as having the cholestatic form When the cases were classified into serum hepatitis and infective hepatitis according to whether or not the patient had received a transfusion of blood or blood product in the six months preceding the appearance of jaundice, correlations appeared between serum hepatitis and the classical picture and between infective hepatitis and the cholestatic form This, however, was contrary to the results of all previous studies, and further analysis showed that the more probable correlation was between the variety of the disease and the area where it was contracted Thus of the 36 patients with serum hepatitis, of whom only 5 belonged to the cholestatic group, 30 had been transferred with their disease from the Far East, whereas of the 54 patients with infective hepatitis, of whom 21 belonged to the cholestatic group, only 8 were from the Far East and 46 were of local origin All 21 cases of cholestatic hepatitis occurred among the 46 local cases of infective hepatitis which suggests that the local epidemic virus had a remarkable predilection for inducing the cholestatic form of the disease Since no other factors, such as exposure to drugs or toxins, were apparently responsible for this distribution of the cholestatic form, Dubin et al feel justified in attributing it to some special property of the virus The even higher incidence of this form in the epidemic in Delhi described by Smetana [3] can be taken as evidence of widespread distribution of this variant of the infective-hepatitis virus

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[1] Socrates on the Health Service 1960 London THE LANCET Ltd. Pp 102. 5s Obtainable from THE LANCET 7 Adam Street London, W C.2 (postage 5*d*)

[1] Eppinger, E Die Leberkrankheiten. Vienna 1937

[2] Dubin I N, Sullivan, B H Le Golvan, P C Murphy, L C *Amer J Med* 1960 29 55

THE GENE

IN a British Association Granada lecture delivered in London on Sept 27, Dr G W Beadle, professor of biology at the California Institute of Technology, surveyed mechanisms of heredity There seems to be no doubt that it is the cell nucleus that contains the primary hereditary message, the gene being the simplest unit of biological instruction, and some 10^4–10^6 of them being necessarily present in every human egg The only nuclear constituents of sufficient complexity to carry such a message are the proteins (linear polymers of some 20 different amino-acids) and the desoxyribonucleic acids (D N A) (linear polymers of only 4 different nucleotides) Evidence favouring D N A as the carrier arose initially from the demonstration that bacterial transforming factors (which cause a typical inherited change in some pneumococci) were composed almost entirely of D N A ,[4] but perhaps the most direct proof came from a study of a bacterial virus with inheritance characteristics known to be particulate These bacteriophages consist of a protein coat surrounding a core of D N A , and electron microscopy had suggested that the protein coat did not enter the cell during the process of infection The protein coat was therefore labelled with ^{15}N and the D N A with ^{32}P, and it was conclusively shown that only the D N A entered the cell Thus since these viruses have genes, and since only viral D N A entered, the viral genes must be D N A

The double-stranded D N A molecule,[5] where the sequence of nucleotide units in one strand automatically determines the complementary sequence of its partner, gave a clear indication of how accurate replication could occur provided that sufficient energy was available to separate the two strands by some sort of untwisting process [6] There is certainly enough D N A in a single human egg to carry all the required information, for about 10^{10} nucleotide units exist in the 46 chromosomes of the fertilised egg (ignoring the sex chromosomes), and such a number is probably sufficient to encode the contents of some 500 large books

The gene, then, can be thought of as a segment of the D N A chain, perhaps some 1000 nucleotide pairs in size, and the process whereby such a gene may direct the synthesis of an enzyme involves transferring the code to ribonucleic acid (R N A) (known to be associated with the chromosomes at certain times) by some kind of template system The nuclear R N A then passes to the cytoplasm, where it becomes incorporated into the microsomes Special segments of this R N A bind and activate specific aminoacids, which are thereby held in the correct order for the synthesis of the particular enzyme This type of synthesis probably occurs only when the enzyme substrate is present—so providing a necessary control to prevent every cell from undertaking all possible syntheses In this way differentiation may be controlled by environment A clear example of such genetic control of enzyme synthesis is the inherited condition of galactosæmia, where the patient wholly lacks the enzyme which changes galactose into a usable form

Mutations can be thought of as alterations of the sequence of nucleotides in the genic D N A either chemically (for example, nitrous acid changes D N A amino groups into hydroxyl groups and so upsets the hydrogen bonding on which accurate replication is thought to depend) or spontaneously under the influence of natural radiations Only occasionally, however, does such a mutation lead to an organism of increased reproductive fitness and so to a permanent evolutionary change

Professor Beadle ended by suggesting that paths now seem open, beginning with a universe of hydrogen, to an evolution through other elements, simple inorganic and then organic compounds, then through more complex organic systems to polynucleotides and proteins, the simple virus-like molecules, simple cellular systems, and finally to man himself

FROZEN BLOOD FOR TRANSFUSION

THE Cohn fractionator [1] is designed to separate individual half-litre units of blood into the component parts—red cells, platelets, and plasma—and to wash the red cells free from plasma It consists of a bowl centrifuge whose temperature can be kept constant, and whose bowl and associated containers can be sterilised Haynes et al have been using this machine for the long-term preservation of blood for transfusion The cells are washed with solutions containing up to 50% glycerin, then frozen at −80°C or −120°C, and after storage for 1 to 44 months thawed, deglycerinised, and reconstituted with an appropriate diluent According to requirements, the cells can be resuspended in saline, their own serum which has also been frozen, or 5% human albumin in an isotonic salt solution, to which can be added, as needed, buffers, globulin fractions, or components of clotting systems Of the red cells taken from the donor, 82% reach the recipient, and these seem to survive in his circulation as long as fresh cells Results have been so satisfactory that this frozen and reconstituted blood has been in routine use at the U S Naval Hospital in Chelsea, Mass , for more than a year So far over 1000 units have been administered without trouble, Haynes et al remark that febrile reactions have been remarkably few, and hepatitis has been absent

The cost of these benefits is considerable Rough costing suggests a figure of about £6 per unit, excluding building and heating, and a team of six workers using two fractionators can process only 200 units monthly. Many London hospitals, dealing with 15,000–20,000 inpatients a year, may need over 500 units of blood in a month. This would call for five fractionators and a team of twelve or fifteen, besides the existing staff of two technicians and a part-time doctor. The cost of each bottle of blood for transfusion would rise from the present £1 2s–1 5s to something like £6–7. Further, such hospitals use blood chiefly to treat unexpected hæmorrhage, relatively little blood is used for elective surgery or for the treatment of anæmia, so a large supply of fresh, or already reconstituted, blood would have to be kept on hand. Now that the incidence of post-transfusional hepatitis has been reduced to 1 in about 800 transfusions, there seems to be little point in providing this expensive equipment for individual hospitals.

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[3] Smetana, H F in Hepatitis Frontiers Boston 1957

[4] Avery, O T , McLeod, C M , McCarty, M *J exp Med* 1944, 79, 137

[5] See *Lancet*, 1959 ii 655

[6] Watson, J D Crick, F J C *Nature Lond* 1953, 171, 964

[1] Cohn, E J Proceedings of the fourth annual meeting of the American Association of Blood Banks, 1951

[2] Haynes L L , Tullis J L , Pyle, H M , Sproul, M T , Wallach, S , Turville, W C *J Amer med Ass* 1960, 173, 1657

On the other hand, there may be a case for setting up a few processing units for blood of unusual groups. Very rare red cells such as -D-, could be reserved against need, and a moderate stock of blood of the less common groups which may be needed for extracorporeal circulations could be established. In the past few months, because many regular donors have been on holiday, there has been a shortage of blood of all kinds,[3] which fortunately has led to nothing more serious than the postponement of elective operations for a week or two, it might be possible to store blood collected in the autumn, winter, and spring against the needs of the summer. But such a project is bound to be expensive, and it is doubtful whether it would produce more benefits than would half the money spent on something else.

SHINGLES AND CHICKENPOX

Wesselhoeft,[4] in delivering the sixteenth Charles Value Chapin oration, took the opportunity to review past and present ideas about the nature of chickenpox and shingles, and gathered into a valuable bibliography accounts of experiments and observations from many sources. Those who thought that Weller and Coons [5,6] in the laboratory, and Hope-Simpson [7] in the field, had convinced the medical profession of the unitary nature of varicella, however contracted, may be disappointed by the note of agnosticism on which he ended his address.

The journals tend to give more space to rare than to common events, and this predominance may disturb the balance of a comprehensive review. Rare occurrences are informative and must not be dismissed, but, still less, the common pattern of behaviour of a disease should not be overlooked. There is a real danger of missing the wood for the trees, especially rare trees.

The common relation between shingles and chickenpox is as follows. Both can cause chickenpox in susceptible contacts, though the risk of this happening after contact with shingles is less than a third of its happening after contact with chickenpox. In either case the resultant disease is, by clinical, epidemiological, and virological criteria, ordinary chickenpox. On the other hand, neither chickenpox nor shingles gives rise to an attack of shingles in contacts, whatever their previous history of either disease. This is the usual pattern shorn of rare exceptions, and it determines the epidemiological behaviour found in practice—namely, that chickenpox appears in epidemics when aggregations of susceptible persons are effectively exposed to cases of chickenpox or shingles, but that shingles does not itself appear in epidemics and is independent of epidemics of chickenpox.

For the "dualist" who holds that there is a distinction between ordinary and zoster-induced varicella there is a difficulty that seems never to have been adequately considered. How far backwards must the antecedents of a case of chickenpox be traced before it can with certainty be classified as "ordinary" and not "zoster-induced"? Are ten generations of ancestry to be considered adequate evidence, or a hundred or a thousand? One observer traced back an outbreak for twelve months and classed it as "ordinary varicella". Had he, by pushing the inquiry still further into the past, found that the outbreak in fact stemmed from an original case of shingles, he would have been compelled to reclassify it as one of "zoster-induced varicella". Except in remote areas it is seldom possible to back-track in this way with any certitude, and, in such remote regions, outbreaks are commonly found to stem either from a local case of shingles or from a case of chickenpox imported from more crowded areas where further investigation of the lineage of the virus is difficult. On all the evidence, it should surely be conceded that there is only one chickenpox, which can be caught either from another case of chickenpox or from a case of shingles.

Much remains to be understood, foremost the nature of shingles itself. If, as seems likely, it is due to the reactivation of latent chickenpox virus, where in the body is the latent remnant? Do all who have had chickenpox depend upon the survival of this latent brood for the preservation of their immunity? How is the symbiosis disturbed so that a harmony of maybe fifty years breaks down, the eruption develops in a dermatome, and infectious chickenpox virus escapes into the environment? On questions such as these light may be shed by the more unusual happenings, the anomalies and exceptions to the common pattern described above. The least uncommon anomaly is the occurrence, usually in children, of a zoster during a primary attack of chickenpox—an apparent exception to the rule that contact with chickenpox does not give rise to shingles. Much rarer are those cases in which shingles in an adult appears to have been caused by contact with another case of shingles or a case of chickenpox. How uncommon this is was shown by a prospective study of thousands of contacts of cases of chickenpox and shingles of whom not one developed shingles. Nevertheless cases have occasionally been recorded in circumstances that make them very unlikely to be fortuitous. Again there are a few records of attacks of zoster-induced varicella failing to protect against subsequent exposure to chickenpox. All such rarities must find their explanation in a more complete understanding of the two diseases, but in the meantime they should not be allowed to obscure the picture which is already emerging.

Even if some laboratory refinement should in the future discover a recognisable peculiarity of virus newly released by an attack of shingles from its intracellular confinement, the interesting observation would no more disturb the ætiological picture than a similar finding in spirochætes from late cases of syphilis would unsettle our present conception of that disease.

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[3] See Graham-Stewart C. W. *Lancet*, Aug. 20 1960 p 421

[4] Wesselhoeft C *R.I. med J* 1957 40 357

[5] Weller T H *Proc Soc exp Biol N.Y.* 1953 83 340

[6] Weller T H. Coons A. H *ibid* 1954 86 789

[7] Hope-Simpson R. E. *Lancet* 1954 ii 1299

The Wider World

MEDICINE AND THE NEW AFRICA *

The Passing of Colonialism South of the Sahara

H S GEAR
M D, B Sc W'srand, D P H, D T M & H
FORMERLY CHAIRMAN, EXECUTIVE BOARD, WORLD HEALTH ORGANISATION, DEPUTY CHIEF HEALTH OFFICER, UNION OF SOUTH AFRICA

Africa south of the Sahara forms a unit of countries with many common features Because of early remoteness, climate, and disease, it was until lately isolated from Europe, and so lacks written history Its peoples—Bantu, Negro, Hamite—have many common physical and social characteristics It is the Africa of the tropics and semi-tropics, with desert, jungle, heat, and sun obtrusive It has been the region of the world most affected by European colonialism It has had an evil name because of the men, especially those coming from temperate lands, who have been killed or disabled by its sicknesses

European influences were first brought to the continent by explorers, missionaries, traders, and prospectors In the 19th century the Colonial Powers, scrambling after them, launched tribal Africa into the Western way of life, and brought it precipitately into the material and technological world created by the Industrial Revolution Through the colonial agents of this world phenomenon, Africa was in time largely freed from the blight of tribal massacres, slavery, starvation, and epidemic disease

Today Africa is impatiently grasping the outward forms of sovereignty More than half her peoples will achieve political independence this year, and before the decade is well advanced the rest will almost certainly have followed Colonialism will then have vanished and new, and largely inexperienced, States will be struggling with the daunting social problems of emerging millions This fact, partly political though it may be, directly affects the future of medicine in Africa

The astonishing reduction in the amount of disease during the past 60 years has been possible because colonialism gave Africa a phase of social stability with a rising economy, and the whole paraphernalia of good central and local civil administration Western medicine had then its opportunity to prevent and cure disease "en masse"

Western ideas have moulded the form medicine has taken both in sovereign countries like the Union of South Africa and the Federation of Rhodesia and Nyasaland, as well as in the Colonial territories of Belgium, France, Portugal, and the United Kingdom In this medicine there has been a significant place for the medical missionary, the private practitioner, the medical professional association, the autonomous university with its medical school, and the public but unofficial research institution It has been a medical system constantly nourished and refreshed from the European home countries

But, though this European form of medicine has given a place to the non-governmental and the non-official, most medicine in Africa has a strong official character The hospital and clinic services of South Africa and the Federation and the general Colonial Services, despite their Western origin, are largely official and depend on Government funds for providing free or subsidised services

If the future held no other obstacles, the official nature of most of the developing African medical systems would create difficulties enough This official bias will be continued by most forms of external aid It makes uneasy those who would like to see the individual doctor and the non-official organisation claim a worthy place

Medicine, in a full sense, today only achieves results if there is an adequate community with law and order, efficient civil administration, good communications, and a sound economy In other words the good health of a community needs not only good doctors, but also well-run cities, villages, and country districts with sufficient food, pure water, efficient waste-disposal, proper housing, and all the other advantages of good government Inevitably the changing political and social scene in Africa will alter the future of medical and other public services

UNITED NATIONS AID

The New Africa is being moulded by external as well as internal forces The most important stimulus comes from the United Nations family, with the World Health Organisation as the agent responsible for health and medicine It is perhaps not fully realised how great a change is being wrought by the United Nations agencies, even though they are intergovernmental and not super-governmental organisations

Delegates from African States appear in ever-growing numbers in the councils of the world and many already have been effective office-bearers African regional and other offices already represent the U N Economic Commission for Africa, the U N Technical Assistance Administration, the Food and Agriculture Organisation, the World Health Organisation, and the U N Children's Fund Most of these directly or indirectly affect health programmes, and as a group are not insignificant in power and resources

A stream of people—consultants, technical experts, advisers, and others—are being directed by the U N group into Africa Another stream flows out carrying delegates, committee representatives, and postgraduate fellows and students

People moving in and out of Africa as part of its technical and scientific evolution are not a novelty But there is something very different about the flow sponsored by the United Nations family The volume is more impressive and it is directed to and from many more countries U N consultants and technical experts now working in Africa come not only from the United Kingdom, France, and the other colonial countries, but from North and South America, the whole of Europe, and several Asian countries The Africans travelling overseas for experience and training also visit a much wider range of countries

The technical aid in medical fields is massive It is gladly accepted by the new African States without the undue sensitivity they sometimes show to aid offered by individual foreign Governments As a result, the organisation of hospital services and clinics, and the training of doctors, nurses, and other staffs have been speeded up

A fundamental principle in this form of external technical aid is to be noted Since the United Nations system is official and intergovernmental, it works through national governmental services It is thus a force which quite properly creates and strengthens official and governmental services in the countries it helps It is supporting officialdom everywhere, and will increasingly do so in the future African medical and other services This is satisfactory provided non-governmental organisations and arrangements are not neglected

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* Based on a lecture delivered under the auspices of the Institute for the Study of Man in Africa, Johannesburg, on June 14, 1960

OTHER INTERGOVERNMENTAL ARRANGEMENTS

The passing of direct colonial control and the arrival of United Nations technical aid do not mean that the Colonial Powers have given up all responsibility for emerging Africa They are helping in the development of such things as general administrative services, universities, hospitals, rural clinics, research institutions, water-supplies, and roads Their hope is that if the new countries have sound public services the transfer of authority to peoples who, though politically active, are on the whole administratively and technically inexperienced will be smoother

It is not only the old Colonial countries which are eager to help the New Africa The Union of South Africa has often and officially stated that it wishes to draw on its own rich technical resources to help the rest of Africa Such help has already been given in many ways

Several South African scientists have visited other African countries, some have served as consultants, a few students from other territories have been trained in the Witwatersrand, Cape Town, and Durban Universities and medical schools, some research teams have worked on general African problems, and the South African Institute for Medical Research is used by many medical services as far away as the Sahara It is also part of several international scientific networks—e g , in virus diseases, spirochætal infections, bilharziasis, malaria, and so on

However, it is doubtful if South Africa yet plays a part proportionate to her technical resources Compared with the many scientists and doctors working in the New Africa who have come from Britain, France, and other European countries, or with the hundreds of undergraduate and postgraduate African students who flock to other medical centres, South Africa seems inactive Yet unless she vigorously develops this two-way exchange of medical scientists and students, her own medicine and science may languish as an international or African force

A more recent feature of intergovernmental technical aid to Africa is the bilateral governmental system Its first great advocate was the United States of America, and Africa has benefited liberally American medical missions are important now in many African states, and there is a steady stream of African students to the great medical and public-health schools of the United States She is keen, too, to cooperate with local groups in research into the many tropical and other diseases which are still difficult to control or treat such as bilharziasis, malnutrition, and many parasitic conditions

But the American bilateral programmes are having some unexpected imitators The Communist countries are already at work in many fields, including medicine, and it is probable that the Chinese will also join in sending technical experts and attracting fellows and students from the African States

NON-GOVERNMENTAL INFLUENCES

The pioneers of Western medicine in Africa, as elsewhere, were not officials but private doctors, and the medical missionary was the pioneer of the pioneers For a hundred years these courageous and selfless people have been among the great medical and social liberators of Africa Their work, generous and independent, goes on Today it is perhaps again critical If tolerated in the new countries, these societies could be a valuable instrument in continuing the spirit and practice of personal and non-official medicine of the best type

It was earlier inevitable, in tropical and tribal Africa, for the Colonial Powers to break the shackles of epidemic and endemic disease by introducing modern medicine through official services So, with the important exceptions of the larger European communities, the private doctor has not been a force

Again, with the exception of South Africa and Southern Rhodesia, medical and nursing professional associations have had an insignificant influence on medical and health policies in Africa compared with the part they have played in Europe and America The professions are generally a sound influence on official ministries, for in considering national health problems they usually hold more than a narrow professional view They contribute wisdom and experience and usually add to the maturity of the community It is, therefore, unfortunate that strong professional associations with a backbone of independent doctors seem unlikely to develop in the newer African States

Yet, paradoxically, one of the dangers threatening medicine in Africa is the private doctor who abandons the ethical code of his profession The charlatan in Africa is already playing on the credulity of the naive and superstitious He may be witch-doctor, masquerading doctor, or qualified practitioner prostituting his calling The new States, therefore, have a clear responsibility to protect their people from exploitation But the State will not succeed in this aim without a medical profession of the highest integrity keen to keep its own house in order

Industry has also contributed to African medicine Most large industrial organisations have acknowledged their obligation to protect the health of their communities In the gold, copper, and trading industries of South Africa, the Rhodesias, the Congo, and West Africa hundreds of thousands of workers are given health and good physique and learn much about keeping themselves fit during the years of their employment Much of this knowledge diffuses into the kraals and villages Hence the position of industry in the new States is of concern to medicine If they accept that private industry can contribute to the economy, this will open a useful opportunity for non-governmental medicine

Another non-governmental agent which could do immeasurable good for medicine in the New Africa is the large philanthropic or public Foundation In Africa the Rockefeller and other American foundations have been joined by the Nuffield Foundation, whose support for the establishment of a vigorous and modern medical school in Salisbury is likely to be one of the germinal events in Central African medicine As Africa changes from colonialism, the great Foundations, both American and British, will have an opportunity of service greater than in the past They are altruistic, objective, generous, and free of politics and bureaucracy They thus can balance the help coming to Africa from the intergovernmental agencies—multilateral or bilateral—with the best type of non-governmental support It will be unfortunate if the new States are unwilling to invite the Foundations to help in the large new medical, technical, and social programmes for which they will soon be responsible

A final example of non-governmental health and medicine is the voluntary organisation In South Africa and the Rhodesias, and to a lesser extent in the Colonial Territories, such bodies have been valuable, and it is to be hoped that the New Africa will encourage the work of voluntary groups, particularly in child and maternal health, first-aid, accident prevention, and social welfare But many circumstances are against them, especially if the new States loosen their Western relationships

SOCIAL TRANSFORMATION

The New Africa to which medicine must adjust itself is as much a product of social, including economic change as of the more obvious political movements. These social changes—in such things as education, economy, agriculture, industry, science, and communications, and in religion—have been accelerated by the results of Western medicine. The reduction of pestilence, as much as the control of famine and tribal warfare and the abolition of slavery, launched the African social revolution. Now, along with the present political and nationalistic movements, these social forces are influencing the future setting for African health and medicine. Indeed the replacement of the social customs of tribal Africa, by something modelled on, or influenced by, external ideas and examples, is happening too rapidly for medicine and the other social services to keep pace. Even if these social forces are not diverted or delayed by political troubles, medicine in the New Africa will still have to face problems very different from the old.

One is already ominous—the growth of population. Released from the old checks of slavery, starvation, tribal war, and preventable disease, the annual rate of increase in some territories is already 3%. People are migrating into the towns and factories, and large urban and industrial populations may place an unbearable demand on public, including medical, services. The witch-doctor is no longer supreme. Old fears have gone, so that hospitals and clinics are being swamped, and overworked doctors and nurses are driven to exhaustion. Africa, like most other developing countries, has too many ugly and squalid towns and villages, and yet their inhabitants increase relentlessly to make slums more depressing and dangerous. Only watchful sanitary administration and good fortune seem to explain the relative absence hitherto of serious disease.

Another feature of the social transformation of importance to the medical reformer is the growing emancipation of the African women. In much of Bantu society women still lack freedom and are only slowly training as midwives, nurses, health visitors, or teachers. Sufficiently educated girls are deplorably few to meet the urgent demands of nursing and teaching.

CHANGING PATTERN OF DISEASE AND DISABILITY

Africa's reputation has not yet recovered from the casualties among those who in earlier days came to explore, trade, or fight. Portuguese missions defeated by fever, Mungo Park's expedition ending in disaster, Dutch, Danish, French, and British trading-posts on the West and East coasts enlarging their cemeteries daily, the decimation by typhoid and dysentery of the South African, and by the malaria and dysentery of the East African campaigns of the first world war—these and many more gave a sinister name to the climate and disease of Africa.

Before medical science unravelled the maze of tropical disease, the hazards of Africa seemed to lie in its malignant climate. Sun, swamp, heat, miasma—all were accused. However, recognition of the true situation has seen the dramatic conquest of most of Africa's pestilential and tropical diseases. Not only is the indigenous African population doubling itself every 30–40 years, but European families are living happily and healthily even in such dreaded areas as the West Coast and the Central African Valleys. If one of the 18th or 19th-century Europeans returned, he would perhaps be chiefly amazed by the contempt of the moderns for the huge pith helmet, red spinal pad, and abdominal or cholera belt which he considered an essential protection against the baleful African sun and climate.

Today we have gone a long way towards separating the climatic and environmental from the communicable and nutritional factors in the cause of African disease. The greatest triumphs were the discovery of the causes and methods of treatment and control of the tropical fevers. The devastating epidemic and endemic diseases of previous centuries are now cowed. Yellow fever, malaria, sleeping-sickness, smallpox, dengue, yaws, and many more are shadows of their former selves. The blame placed on tropical and African climate is now known to have been much exaggerated. Now we know that an efficient sanitary system and a good diet can make nearly all Africa tolerable and healthy.

Formerly nearly all the dangers to life lay in communicable disease carried by insects or infected food or water. Climate was indirectly responsible in that it gave these diseases the medium for their propagation. With disease reduced or eliminated, tropical climates become themselves less fearsome, if still uncomfortable. Today we know much about the direct effects of sunlight, heat, and humidity. Unpleasant though extremes of these may be, their effects can be borne more tolerably by applying the present knowledge of the human body's capacity for acclimatisation and adjustment. Much of this work was shown on the Witwatersrand—e.g., the regime of adjustment to work, environment, heat, and humidity applied in the mines. The human power of physiological adaptation, combined with modern housing and work places, and, if necessary, air-conditioning, is radically changing the medical view of the future capacity of Africa to support healthy human populations even in its more fearsome desert and jungle regions.

With the astonishing decline of the pestilences a new pattern of diseases is appearing. Some of these diseases have always existed but were overshadowed. Others seem to be truly new, or much more virulent. Others are a product of social change.

Examples of diseases now more prominent by contrast are malnutrition and some of the dysenteries. Mass famine is now rarely seen, but protein malnutrition has lately been recognised as widespread. Infantile diarrhœa persists as a serious public-health hazard.

A group of diseases partly old and previous unrecognised, and perhaps partly new or more virulent, is those caused by viruses. Besides such well-known viruses as those of poliomyelitis, influenza, and trachoma, a whole host of new agents has been found in Africa. Much of this research has been done in the South African Poliomyelitis Foundation supported by a team from the Rockefeller Foundation.

Two examples of conditions aggravated by the stresses in a society shifting from the pastoral to the modern are tuberculosis and industrial disease. Unfortunately tuberculosis is increasing in nearly all African territories, especially in the town and labouring groups. The story of industrial expansion in other continents is unhappily repeated. Again, increasingly as the New Africa becomes industrialised, the problems of disease in mines and factories will arise, especially if the vigilance of the national health and labour administrations slackens.

Modern life is not only putting people into factories and towns, it is altering the agricultural scene. More and more large-scale agriculture in Africa is dependent upon irrigation. This is spreading bilharziasis and making the control of its snail vector more difficult. Several other parasitic worm diseases and intestinal infections continue to cause much sickness and inefficiency throughout tropical areas. Their reduction must await improved sanitary services and higher personal standards of cleanliness.

In the new pattern of disease one feature is becoming more and more striking—accidents Even in remote regions of Africa accidental injuries are serious Every new road brings an almost incredible number of car and lorry fatalities and cripplings In New Africa, as in the rest of the world, the accident of the home, road, and factory is killing and maiming people and filling hospitals in ever larger numbers

As the acute diseases recede and as the chance of living longer in a modern world increases, the so-called chronic degenerative conditions obtrude themselves Here, too, Africa shows signs of copying the world design Whatever may be the full story of their causes and associations the melancholy record in more and more countries is of death and disability from heart and kidney disease, nerve degenerations, and malignant disease The mental afflictions, too, will probably be more obvious in the future Africa

WHAT PATTERN FOR MEDICINE?

The speed and confusion of events are unfavourable to prophecy, but once the transition to sovereignty is achieved and a new African political condition is created, what will be the philosophy and form of its medicine?

In an immediate technical sense there will be enormous tasks to shoulder The prospects of rewarding careers will lie before the new African doctors and nurses—suffering to be relieved, premature mortality to be challenged, fuller and healthier lives to be sought for the growing millions They will also have an enviable opportunity to probe many remaining mysteries in disease They will be the privileged observers of the whole gigantic phenomenon of a people being changed by social pressure to accept new ways of life Such tantalising questions as the effects of climate and environment on energy, mental capacity, physiological efficiency will be theirs to study Medicine in the New Africa will be rich in obligation and in opportunity for research

Public-health and preventive medical measures to meet the challenge will only be effective, indeed possible, if the general administration is competent But even assuming that no disastrous weakness appears in the public-health organisations of the New Africa, its future medical philosophy is still uncertain

Medicine at its best is something finer than an exercise of technical skill In the medicine being introduced into Africa and other developing regions this broader duty is too often neglected Yet here the need is more desperate than in the older lands where all upbringing supports understanding of such social responsibilities The culture and civilisation which have produced modern medicine, and of which it can be a noble component, are also essential in the new countries if they are to gain completely Medicine's true teachers and disciples give more to Africa than medical care in a hospital or clinic Their integrity and philosophy are a demonstration of the goodness to be found in their culture This is necessary if the struggling new African medicine is to be something more than a mere materialistic technique or rival to tribal witchcraft, which could easily revive under a cloak of African nationalism

Western medicine in helping Africa should not overlook the need for this broader interpretation of its possible service It should guide Africa to create people who are good doctors and nurses, but are also prepared to follow fearlessly the principles founded over many difficult generations in Europe and America This responsibility will be more onerous in New Africa than in the older settled communities of Europe and America But the future African doctor, by being a man of integrity and principle, will increase the stability of his country and the respect it will earn in the world

Special Articles

THE MINISTER ON THE HEALTH SERVICE

Mr Enoch Powell, Minister of Health, reviewed the structure of the National Health Service in an address to a joint meeting of the English and Welsh Executive Councils Associations at Llandudno on Oct 27 He said

> "The National Health Service, by its very nature as a comprehensive State service, holds out dangers and possibilities of harm as well as opportunities and possibilities for good We can never wholly eliminate the risks and be left with only the opportunities What we have to do is to discern as clearly as possible where those risks lurk and what they are We shall then be in the best position to counteract and minimise them"

The service was the channel through which flowed the overwhelmingly large proportion of our national income which we devoted to the care of health and the treatment of the sick The fraction so devoted had not, on average, been much larger during the last decade than it was twenty years earlier—though, of course, the national income itself had been larger and so, consequently, had been the absolute amount of resources devoted to medical care One thing was certain as our national income continued to rise, the volume of effort and resources devoted to health would rise Another thing, too, was certain—that with the inevitable changes in the texture of society and in the content of medical knowledge and theory, the nature of the resources and the application of the effort devoted to health would also alter In any given state of society and medical knowledge there was an ideal application of the available resources which would yield the greatest harvest in terms of health, wellbeing, comfort, reassurance—in short, of happiness We should never quite attain this ideal, but we ought always to be tending towards it, and success or failure in doing so depended on the nature and the functioning of the channels through which the available resources flowed Mr Powell continued

> "It is in this context that a comprehensive State service has its dangers In such a service responsibility is inevitably centralised—in the Minister answerable in Parliament Because responsibility is centralised, so, in large measure, must be decision, since responsibility implies the power to take the decisions for which one is answerable This in turn implies an administrative machine which will link all the parts together and secure conformity with the central policy and decisions Now, all this brings with it a great danger—that of rigidity Policies which are formed centrally and executed administratively are bound to be slower to change and less adaptable to alterations of circumstance and demand than if responsibility were diffused and decisions were independent The great machine is bound to have a one-track mind, to be cumbrous and unresponsive, to abhor variations, to be insensitive to the world around it
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> "These disadvantages apply anywhere, but in the field of health and medical care they can be specially dangerous Here is a field in which it is the individual mind, the local experiment, even the chance observation, which bring about the great advances The man or woman who is (as we say) before

his time, at whom officialdom is bound to look askance, whom contemporaries treat as an oddity or a nuisance, turns out to be the pioneer, doing the work which determines the direction of future development These people need an environment in which they have opportunity, even encouragement, certainly not repression But how is the machine to know them when it sees them ?"

Not only the methods of giving medical care, but the character of the need for it were constantly changing Post-war legislation and planning for all the welfare services reflected the conditions of the pre-war world for it had nothing else to go on They were trying now to assess the revolution of the 1950s, but it might be far into the 1970s before they could adjust the machinery to take account of it This conflict between the characteristics of a comprehensive State service and the facts of social change and medical progress could never be fully resolved, for it was inherent But by recognising it, there was much they could do to limit and counteract its dangers

Those who framed and hammered out the National Health Service were not unconscious of the dangers, and they deliberately embodied in its structure elements of independence, both lay and professional, to be a counterpoise The contractual status of the general practitioners, dentists, and opticians, the separate representation of the doctors and other professions in the structure of the hospital and executive council services, the power and authority of the professional colleges and associations—these might seem to have a fine old English illogicality in a State service "But a wise Minister of Health will see in them not hindrances but safeguards to the soundness of his work, and in all that I do or seek to do I shall be as jealous of the independence of the professions as they are themselves," said Mr Powell

But all these built-in counterpoises in the structure of the National Health Service to the dangers of the great machine would not be sufficient if the great machine itself were all "The National Health Service is intended to be comprehensive, it is not in my view intended to be exclusive," went on Mr Powell "For the service's own sake, I attach the highest value to the fact that medical service and care is also available outside it and that completely independent organisations exist in the field, to support and conduct research, to study and criticise, to supplement, assist, and (why not ?) overlap the services provided by authority of Parliament" He welcomed the flexibility and spontaneity which these other channels bring to the nation's provision for health

Mr Powell recognised three trends in the modern approach to health and medical care (1) the growth of community care and aftercare of the sick, "which takes off the hospitals work which can be done more effectively and more beneficially outside them", (2) the development of preventive and remedial measures which will prevent admission to hospital or lengthy treatment there, and (3) the more intensive and efficient use of hospital accommodation, expressing itself in higher turnover of patients and lower ratio of beds to population In two of these three the initiative in development lay with the local authorities, and if the new trends were to find full expression, the biggest expansion within the health service in the next decade would have to come on the side of local government One should note finally that as the link between the three trends is, from one point of view, the patient as an individual human being, so the link from another point of view is the friend and adviser of the patient as an individual human being—namely, the general practitioner

Turning to finance, Mr Powell declared that the financial structure of the National Health Service could not have been devised more effectually if the object had been to put the three main elements into watertight, non-communicating compartments There were in fact three separate financial systems, and consequently the interrelation between developments and decisions in each of the three fields was virtually impossible to express in the clear financial terms which would so much help administration and public understanding "However, I must say bluntly that a major reform in the financial structure of the National Health Service is farther off at present than the eye of a politician can see We must work with the structure we have got, and I shall not be content until I can see a long-term picture in which the development of the hospital service is dovetailed with the development of the local-authority services, and the future function of the family practitioner is related to both"

Dialogues of Today

SOCRATES, THIS IS YOUR LIFE!

HAEMON Come in, Socrates, and don't be surprised to see so many people We know that you are becoming an author yourself for the first time, so we thought we would like to congratulate you Socrates, this is your life!

SOCRATES It is true, Haemon, that I am no longer to be dependent upon Plato and Xenophon for an account of my words, but I am no author any ideas to be found in my conversations are contributed by those with whom I talk I am only a midwife, delivering other people of their ideas

HAEMON Come in, Apollodorus, and tell us how you first met Socrates

SOCRATES Welcome Apollodorus! What have you been doing today ?

APOLLODORUS I have been in court arguing as to whether or not certain words are obscene

SOCRATES Is there any more important question ?

APOLLODORUS I should hardly have called it important, Socrates

SOCRATES But tell me, is not obscenity sometimes a kind of swearing ?

APOLLODORUS Sometimes it is

SOCRATES And when men swear do they not use words, which are held sacred, in a way which is considered blasphemous ?

APOLLODORUS Certainly

SOCRATES It would seem then that if we are to decide why words are obscene we must also consider what makes words sacred, and we can hardly do that without asking what is sacred, and why it is so So you see why I said that the nature of obscenity is a most important question But, tell me, is there any characteristic of the obscene words themselves which distinguishes them from other words ?

APOLLODORUS I don't know of any

SOCRATES Are they not all short words, usually of one syllable ?

APOLLODORUS I suppose that is true, but surely it is not the form of the word but the meaning which renders it obscene

SOCRATES Surely not, Apollodorus, for if instead of a word of four letters you use an equivalent one of four syllables, the feelings of your hearer will be quite different, although the meaning is the same Does it not seem to you that a short word contains all its energy in a small space and at high tension, and at once conveys to us a physical reality, whereas a word of four syllables carries its energy at low tension, and so conveys a meaning which is emotionally diluted, and makes far less impression on the feelings?

HAEMON Thank you Apollodorus! Now here is Analyticus

SOCRATES It is appropriate that you should have come just now Analyticus, when we are talking about obscenity, for are there not many people who think all your writings obscene, even though you use many words of more than four syllables?

ANALYTICUS Yes, indeed, Socrates, but when I am called a corrupter of youth I console myself with the fact that they call you the same.

SOCRATES Tell us why you think some words are obscene.

ANALYTICUS I think the form of the word is only one factor, important though it is A word may transmit emotion forcibly, but the emotion is related to the thing signified If some things were not sacred swearing would lose its point, but so it would if it were not considered reprehensible, and it is reprehensible only because some things are sacred. People sometimes speak of obscenity as animalism, but that is just what it is not Animals alone are innocent of obscenity Obscenity implies a sense of guilt. If you never swear you are either perfectly balanced or too conscious of your own guilt

HAEMON Here is Eryximachus

SOCRATES Welcome, Eryximachus, for there is no one more fitted than you to explain to us the nature of obscenity, since no one behaves more shamelessly than you.

ERYXIMACHUS How is that, Socrates?

SOCRATES Do you not discuss with your patients matters which they would be ashamed to talk about with anyone but a doctor, and when you examine them do you not insist that they should conceal nothing which their modesty makes them conceal from others? And in all this do either you or your patients feel any shame?

ERYXIMACHUS But there is nothing obscene in all that, Socrates, for modesty is a matter of convention and shame does not arise in the relation between doctor and patient

SOCRATES It is the same with me, for I am not only a midwife who delivers men of their ideas, I am also a physician who seeks to examine their thoughts in all their nakedness and a surgeon who practises the orthopædics of the mind And it is my aim to examine men's words and to persuade them to let them be examined in the same spirit of truth with which Eryximachus examines their bodies

HAEMON I am sure we all wish your book the success it deserves Socrates, master of words, this is

XANTHIPPE (*marching firmly into the room*) your wife! I'll give you words! Was there ever such a man? He hasn't slept for two nights, yet here he is talking about words And he drinks twice as much as anyone else without getting drunk, and sleeps out of doors wherever he finds himself, without even a blanket. But what does any of you care so long as you can get him to discuss philosophy? I'll give you a bit of philosophy Where do his words come from? Where does his life come from? Ultimately from my kitchen Think that one out, all of you! Come on, Socrates, we're going home

(*They go*)

The Widdicombe File

LXVI.—THE DIVISION OF PATHOLOGISTS

DEAR PETER,

I thought your letter* was a very sound and moderate statement of the case—as stated by a supporter of a Faculty with the Physicians Of course you were trying to be impartial, just as every decent pathologist tries to be when he rehearses the arguments, but it is just impossible. The only man who can be truly impartial is the man who does not care one way or the other, and he will not trouble to rehearse the arguments at all That presidential address which you rightly describe as statesmanlike was, I know, meant to be impartial, but to me the final section seems to emphasise the advantages of a Faculty and the disadvantages of a College

You have recited some of the arguments for and against both sides, and I would like to review some of them as a supporter of the College You quote the argument that the establishment of a College "would be a cripplingly expensive undertaking", but this is obviously untrue unless we develop delusions of grandeur and try to obtain in a few years the sort of accommodation which other colleges have taken centuries to build up The independent Faculty of Radiologists, which is doing for radiology what a College would be trying to do for pathology in its early years, is able to exist simply and economically, and so could we You quote the argument that any examination set up by the College would take many years to achieve recognition, but what is the evidence to support this view? There is after all no really satisfactory examination at present for would-be consultant clinical pathologists, and if a College of Pathologists provides a good one I can see no reason why it should not quickly become accepted

As for the College of Physicians, it is difficult to consider it as anything but what the name implies, even though I agree that it is not exclusive, and accept that out of every 100 "active Fellows" there are about 11 administrators, 9 pathologists, 6 academic pharmacologists, physiologists, or research-workers, 2 radiologists, and an obstetrician It could, of course, cease to be primarily a physician's college, but is that the wish of most physicians? I would agree that most clinical pathologists, if they had taken up any other specialty, would probably have wished to become physicians rather than surgeons or obstetricians But clinical pathologists are still not physicians except in so far as a few hæmatologists have their own patients, and although we certainly must remain *clinical* I see no reason why we should enter into closer relations with the physicians than with any other special group of doctors

"If we were all certain that we could trust the Physicians", you say, "I think few would hesitate to accept their offer" I think you miss the point This is not a matter of trust, but a matter of intelligent anticipation of the possibility that the interests of physicians may not always coincide with those of pathologists If they do, well and good, but suppose they do not? You say that "if, after an honest trial we found ourselves unable to agree with them, nothing could stop the faculty then splitting off" I think you overlook the fact that the Faculty would be a creation of the College of Physicians, not of pathologists, and it could hardly split off as a body unless the parent college chose to abolish the Faculty Are you prepared to envisage a future situation when a body of dissatisfied pathologists has to try to set up an independent college in opposition to an established faculty? Then indeed the "dissensions and bankruptcy" of which you warn us might well become a reality

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* We printed this letter from the File on Oct 22.—ED L

Our seniors often tell us that there is no advantage to them from either course, and that they are only concerned to provide for the younger pathologists in whose hands the future lies At the same time they tend, perhaps, to ignore the experience of most of those who discuss such matters with these younger pathologists, and find that they are mostly in favour of a College The young men do not seem to be afraid of starting in a small way provided that they can feel genuinely independent and not a sort of appendage to another college Their "image" of pathology is of a subject which is of real importance in its own right and which can therefore expect its own separate and individual organisation

If we are to build surely for the future, independence is the only safe choice When I have reached retiring age, I do not want my juniors to be able to say to me "You and your colleagues made a fine mess of things in 1960 Here we are stuck in the College of Physicians where we are not really happy, but it will be very difficult to break away now If you had only made the effort to form a College it would be well established by now Did you *have* to choose the easy way? Couldn't you see just a little way in front of your noses?"

Yours,
G G

Symposium

TICK-BORNE ENCEPHALITIS VIRUSES

FROM A CORRESPONDENT

THE Institute of Virology of the Czechoslovak Academy of Sciences acted as hosts to virologists from eleven different countries during a four-day symposium last month on the biology of viruses of the tick-borne encephalitis complex The meetings were held in delightful surroundings at the House of Scientists at Smolenice, near Bratislava Representatives from almost all the major groups working on this subject were present, and the symposium provided an unusual opportunity for workers from many different disciplines to pool information and exchange ideas in a common approach In Britain, human infections with louping-ill virus do not present a serious public-health problem, but in Central Europe, Scandinavia, U S S R, and India viruses of the tick-borne encephalitis group are a serious menace The recent recognition of human infections with viruses of this group in Canada[1 2] and the U S A[3] extends the area in which these viruses are known

Dr J Casals (New York) showed how the tick-borne viruses were placed with yellow fever and some twenty other arthropod-borne viruses into the serological group B on the basis of antigenic relationships In the past, the tick-borne encephalitis viruses have been considered a homogeneous group in spite of wide differences in the disease patterns they produced in different parts of the world Dr D H Clarke (New York) showed that they could be divided into six antigenic subgroups on the basis of hæmagglutination inhibition tests with absorbed sera and by agar-gel precipitin tests The six subgroups were represented by the classical far-eastern Russian spring-summer encephalitis (R S S E), louping ill, Omsk hæmorrhagic fever, Kyasanur Forest disease,[4] Malayan tick-borne Langat virus, and Central European tick-borne encephalitis which included Czechoslovakian, Austrian, Finnish, Polish, Swedish, and Yugoslavian strains, as well as strains from European U S S R The recently described North American Powassan virus had not yet been examined by these techniques These antigenic differences were important because they explained the reported failure of R S S E vaccine to protect humans (Dr P N Bhatt, Poona) or mice (Dr L Daneš, Prague) against infection with the virus of Kyasanur Forest disease

As in other branches of virology, tissue-culture techniques were gradually replacing older methods for the titration of viruses and for the detection of neutralising antibodies The use of a plaque technique for the titration of tick-borne encephalitis viruses was described by Dr J S Porterfield (London) and was applied by Dr V Mayer, Dr J Zavadá, and Dr R Škoda (Bratislava) to Central European strains Dr Bhatt reported that chick fibroblast cultures were as satisfactory as mice for the primary isolation of Kyasanur Forest disease virus Czechoslovak workers preferred a two-stage process—primary isolation in tissue-culture cells which were later shown to be infected by virtue of their resistance to a challenge virus Neutralising antibodies were detected by a metabolic inhibition test carried out in Hela cells (Dr H Líbiková and Dr J Vilček, Bratislava), by plaque inhibition (Dr J S Porterfield, London), or by the direct inhibition of cytopathic effect in Hela cells (Dr E Molnar, Budapest) or in pig kidney cells (Dr D Málková, Dr Z Marhoul, Dr V Fraňková, and Dr V Černy, Prague)

Vaccines derived from formalinised mouse brain had been used for many years in the U S S R (Prof E N Levkovich, Moscow, Prof A A Smorodinstev, and Dr V I Ilyenko, Leningrad) and formalin-inactivated louping-ill vaccine had been used to protect laboratory personnel (Dr D G ff Edward, Beckenham) and domestic animals (Dr D Blascovic and others, Bratislava) Attempts at producing a vaccine from virus grown in tissue culture were reported from Prague (Dr R Benda and Dr Danes), from Budapest (Dr E Molnar), and from the U S S R The major difficulty was to guarantee complete destruction of infectivity without at the same time reducing the antigenicity of the vaccine There were many parallels with the poliomyelitis vaccine problems A further important factor reported by Dr G D Zasukhina (Moscow) was that virus grown in tissue culture with a deficient medium was less antigenic than virus grown in a rich medium

The maintenance of the tick-borne viruses in Nature is still not completely understood The course of infection in an experimental animal, the laboratory mouse, was studied by Dr P Albrecht (Bratislava) in an elegant series of experiments based on the use of fluorescent antibody techniques Other animals which may be infected in Nature include bats and lizards (Dr J Rehácèk, Dr J Nosek, and Dr M Grešiková, Bratislava), domestic ducks (Dr E Ernek, Bratislava), and coots (Prof H A E van Tongeren, Leiden) Much remains to be learned about the natural history of this group of viruses Although the great majority of infections are transmitted by the bites of infected ticks, mechanical transmission by mosquitoes (Dr Z Zotowski and Dr Z Wroblewska-Mularczykowa, Warsaw) or fleas (Dr K Heyberger, Dr A Smetana, and Dr B Rosicky, Prague) may play some small part in the local spread of infection, and infection by the ingestion of milk from infected goats, sheep, and cattle is now well established The many factors which influence the natural history of viruses of the tick-borne encephalitis complex were ably reviewed by Dr T H Work (New York)

The full proceedings of the symposium will be published by the printing house of the Czechoslovak Academy of Sciences and this volume will be an authoritative summary of all present knowledge of this important group of viruses The organisers are to be congratulated on calling together the participants and drawing forth such a full and lively exchange of ideas

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[1] McClean D M, Donaghue, W L *Canad med Ass J* 1959, 80 708

[2] Casals, J *ibid* 1960, 82, 355

[3] Thomas L A Kennedy, R C, Eklund, C M *Proc Soc exp Biol*, N Y 1960, 104 355

[4] See *Lancet*, Oct 29, 1960, p 988

In England Now

A Running Commentary by Peripatetic Correspondents

ATHEROSCLEROSIS among senior consultants is to be expected nd, within reasonable limits, is perhaps right and proper ut when it strikes among your contemporaries—chaps you were at school with—complacency is shattered. So I bought a icycle, for has it not been clearly shown by the work of whoever it was that exercise and coronaries were negatively orrelated? Admittedly the idea was not entirely my own. Not long ago I chanced on a visiting physician of some eminnce, washing himself down in the hospital cloakroom. He xplained that he had just pedalled over from Fulham, a good ourteen miles away.

Choice of velocipede was easier than I expected, for there was nly one secondhand machine of my size, and when the handlebars had been changed (the old ones scraped the ground) was left with a good bargain. My early experience was alutary. 14 years of motoring had involved different (if any) muscles and the saddle impinged on areas of my big-end which I had long forgotten. Life on the roads as a glorified pedestrian seemed very different from the world of motorists, and it was most unnatural to have to stop at red lights. But I persevered and rode daily to and from hospital. As my reflexes, quadriceps, and some callosities developed appropriately, travelling suddenly became much more interesting. Territory I had motored over a thousand times yielded unnoticed gems of architecture or nuances of gradient. The prevailing wind started to play a part in my life. I turned again to Nature and the basic things of life without which a man's spiritual development cannot take place—such as irritable little dogs, midges, and rain down the back of your neck. Also you get a closer look at blondes in the bus queue. Even securing the aid of a bicycle shop was a new experience, no garage has charged me as little as 2*s* for anything.

Yes, cycling has reopened a dimension in my life. Surprising what a few miles a day will do. My weight is down, muscles are up, wind is longer, mind clearer, and waist more waisted. It has been a wonderful week to recall, as I drive to my hospital with the heater on, listening to the radio.

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The Comet journey to New York was a revelation in quietness, and in the extraordinary deep blue of the sky at 40,000 ft.

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TICK-BORNE ENCEPHALITIS VIRUSES

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Dr J Casals (New York) showed how the tick-borne viruses were placed with yellow fever and some twenty other arthropod-borne viruses into the serological group B on the basis of antigenic relationships In the past, the tick-borne encephalitis viruses have been considered a homogeneous group in spite of wide differences in the disease patterns they produced in different parts of the world Dr D H Clarke (New York) showed that they could be divided into six antigenic subgroups on the basis of hæmagglutination inhibition tests with absorbed sera and by agar-gel precipitin tests The six subgroups were represented by the classical far-eastern Russian spring-summer encephalitis (R S S E), louping ill, Omsk hæmorrhagic fever, Kyasanur Forest disease,[4] Malayan tick-borne Langat virus, and Central European tick-borne encephalitis which included Czechoslovakian, Austrian, Finnish, Polish, Swedish, and Yugoslavian strains, as well as strains from European U S S R The recently described North American Powassan virus had not yet been examined by these techniques These antigenic differences were important because they explained the reported failure of R S S E vaccine to protect humans (Dr P N Bhatt, Poona) or mice (Dr L Daneš, Prague) against infection with the virus of Kyasanur Forest disease

As in other branches of virology, tissue-culture techniques were gradually replacing older methods for the titration of viruses and for the detection of neutralising antibodies The use of a plaque technique for the titration of tick-borne encephalitis viruses was described by Dr J S Porterfield (London) and was applied by Dr V Mayer, Dr J Zavadá, and Dr R Skoda (Bratislava) to Central European strains Dr Bhatt reported that chick fibroblast cultures were as satisfactory as mice for the primary isolation of Kyasanur Forest disease virus Czechoslovak workers preferred a two-stage process—primary isolation in tissue-culture cells which were later shown to be infected by virtue of their resistance to a challenge virus Neutralising antibodies were detected by a metabolic inhibition test carried out in Hela cells (Dr H Líbiková and Dr J Vilček, Bratislava), by plaque inhibition (Dr J S Porterfield, London), or by the direct inhibition of cytopathic effect in Hela cells (Dr E Molnar, Budapest) or in pig kidney cells (Dr D Málková, Dr Z Marhoul, Dr V Fraňková, and Dr V Černy, Prague)

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Choice of velocipede was easier than I expected, for there was only one secondhand machine of my size, and when the handlebars had been changed (the old ones scraped the ground) I was left with a good bargain My early experience was salutary 14 years of motoring had involved different (if any) muscles and the saddle impinged on areas of my big-end which I had long forgotten Life on the roads as a glorified pedestrian seemed very different from the world of motorists, and it was most unnatural to have to stop at red lights But I persevered and rode daily to and from hospital As my reflexes, quadriceps, and some callosities developed appropriately, travelling suddenly became much more interesting Territory I had motored over a thousand times yielded unnoticed gems of architecture or nuances of gradient The prevailing wind started to play a part in my life I turned again to Nature and the basic things of life without which a man's spiritual development cannot take place—such as irritable little dogs, midges, and rain down the back of your neck Also you get a closer look at blondes in the bus queue Even securing the aid of a bicycle shop was a new experience, no garage has charged me as little as 2s for anything

Yes, cycling has reopened a dimension in my life Surprising what a few miles a day will do My weight is down, muscles are up, wind is longer, mind clearer, and waist more waisted. It has been a wonderful week to recall, as I drive to my hospital with the heater on, listening to the radio

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There are times, of course, when I deliberately avoid the title, but my landlady disapproves strongly of any attempts at dissimulation. If people ask for me on the phone as "Miss   " or use my Christian name, I hear her answer sternly, "I'll see if The Doctor is in."

* * *

Comparative textual criticism can be fun. Study of Baedeker's post-war (1958) guide to Austria and the 1929 edition provides a revealing gombarison—sorry, comparison. Though the familiar red cover with gold lettering is retained, it is no longer teutonically tubby but svelte. It contains 294 pages compared to 518, 100 of which were devoted to "Budapest, Prague and the north Bohemian spas", now omitted. (Though Hungary and Czechoslovakia had been independent countries for ten years, one would hardly gather it from the 1929 edition.) The present edition, now called an autoguide, is streamlined in other ways besides format; for instance, we no longer have blow-by-blow accounts of museums and picture-galleries with exhibits thought worthy of notice by Herr Karl mentioned in each room. There is less ancient history and esoteric information; thus we are no longer told that the Dragon Fountain or Lindwurmbrunnen in Klagenfurt is made of "chorite schist" but I was glad to see that the tablet commemorating Emanuel Hermann (1839–1902), "who invented the postcard", is still mentioned. Nor are there detailed tours of each town, starting from the railway station, but much clearer plans with "sight-seeing tours" and "through routes". In fact, modern travel is clearly no longer designed either to broaden the mind or flatten the feet. But nostalgia is catered for by the occasional survival of some of the classical phrases such as "Gasthof Lukashof, plain but well spoken of", still recalling one's aunt or members of the Women's Institute.

* * *

O, my Luve's like a red, red rose.
I hope it's nothing catching.

Letters to the Editor

FUTURE ORGANISATION OF PATHOLOGISTS

SIR,—A voting paper is about to be circulated to pathologists asking them to record their opinion for or against a division of pathology within the Royal College of Physicians, or a new College of Pathology

We have for many years been concerned with research in pathology and with the training of pathologists, and believe that a higher examination based on a background of suitable training is essential to ensure that candidates either for hospital or academic appointments have acquired a reasonable grounding in their subject

We both write as past presidents of the Association of Clinical Pathologists, who have been openly critical of the procrastination of the Royal College, but who are satisfied that the suggestions now put forward by it are what is required Undoubtedly, the Royal College has been unduly tardy in making any suggestions, but the present generous and unequivocal terms make amends

It is generally agreed that in modern conditions the membership is an unsuitable examination for pathologists In the time available the techniques of clinical examination and of pathology cannot both be mastered

We welcome the opportunity of still closer cooperation with our clinical colleagues Not only are they progressively more dependent on us for confirmation of diagnosis, or indeed in many cases for provision of all the important data, but, reciprocally, we also are dependent on their acumen and powers of selection for our daily interests

We have long believed that what is needed is

(1) A higher qualification of the same status as the M R C P and F R C S

(2) An academic centre which would uphold the standards of pathology and help in maintaining good standards of training in pathologists

(3) A body to speak for pathologists

In our opinion the suggestion of the Royal College satisfies these requirements We believe that unless this opportunity is accepted there will be a very long delay before we realise our ambitions

London

JOAN TAYLOR
R J V PULVERTAFT

SIR,—Much has been said and written on this subject by the more learned and senior practitioners of our specialty, but little by the juniors As one of their number may I put forward three points

The primary reason for any alteration in the present position is to ensure recognition of the status of pathologists, despite the fact that a man's status depends above all upon his personality and the quality of his work, and only secondarily upon his qualifications Higher qualifications, however, are necessary to prove adequate training in one's own specialty for promotion to consultant or similar grade, and the institution of a specialist examination in pathology, of the highest standard, is now urgently required To the pathologist in training it is the most important facet of the present discussions The expenditure of time and work by those who aspire to the membership of one of the Royal Colleges of Physicians has been eloquently described by Professor Cappell in his presidential address [1] to the Association of Clinical Pathologists It is certain that only the qualification offered by the Royal College of Physicians will have the immediate high standing required to divert them from such examinations

The finances of the new organisation are of particular interest to impecunious registrars and lecturers It has been said that the provision and maintenance of any reasonable building will cost each member an initial donation of about £100 and an annual subscription of up to £25! Some of us may not be able to find such a sum Are we to be excluded from the college until we are senior enough to afford the subscription, and if so will we ever achieve the seniority? However, we are assured that industry and various benevolent foundations will provide the necessary funds Even if the money is forthcoming, I do not believe we can justify spending such vast sums on establishing a college, when there are so many research projects urgently needing finance Would our money not be better spent on research on acute leukæmia in children or even coronary disease in pathologists than upon a building? £100,000 would buy a lot of knowledge of disease—could we not devote our benefactions (if any) to establishing a series of research fellowships rather than a college?

If a College of Pathology is to be founded then I believe it must be as broadly based as possible and must be open freely to all those who work in and around the subject, scientist or doctor, whether academic or clinical Pathology is neither practised nor advanced solely by those on the Medical Register However, in a Faculty of the Royal College of Physicians it would be logical to restrict full membership to the medically qualified

The College of Physicians of London is a body of the highest standing and to be called a physician is no dishonour I hope, with Peter Davey,[2] that a Faculty will be established They offer us more than does an independent college in the foreseeable future, and at less cost The generosity of their terms puts us in an immensely strong position, and we can always withdraw

Finally, may I suggest abandonment of the term " Division of Pathology ", for the words come uncomfortably close to the truth

London, S W 15 P O'GORMAN

*** Another view on this subject is given on p 1025 in a letter from the Widdicombe File —ED L

ATHEROSCLEROSIS AND CORONARY HEART-DISEASE

SIR,—Surely your correspondents are arguing on points of semantics rather than pathology As you, Sir, rightly pointed out last year,[3] patients do not suffer or die from coronary disease, but from the consequences of myocardial ischæmia, which may be acute, chronic, or spasmodic I have always held that one of the best classifications of disease causation, is that which we learned at our obstetrician's knee, of which a part ran—faults in the powers, faults in the passages, faults in the passenger Myocardial ischæmia may be due to faults in the power of the heart's action, faults in the coronary passages whether narrowed or occluded by what you will, or faults in the passenger—the blood, which may be deficient in oxygen-carrying capacity, or contain a substance noxious to the myocardium

In spite of the welter of investigations on atheroma and degenerative heart-disease, we remain remarkably ignorant as to the frequency, degree, and type of myocardial ischæmic change to be found at death in the population as a whole, and without this many of our deductions in this field are insecure I believe that a study, almost completed here by Dr C J Schwartz and Dr J R A Mitchell, will give us this information, as far as the current Oxford postmortem population is concerned, and may encourage others to carry out comparable investigations elsewhere

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[1] *Lancet*, Oct 15 1960, p 863

[2] See *ibid* Oct 22 1960, p 921

[3] *Lancet* 1959 ii, 863

No-one would dispute that one may find coronary narrowing or occlusion in hearts from persons of all ages, yet it remains that in a high proportion of elderly persons, ischæmic myocardial lesions occur, which are quite different in character from those usually seen in the younger age-groups, for example, there is the condition which Linzbach called reticular myocardial necrosis, but unhappily this is a sphere of cardiac pathology which to a large extent is unexplored

Turning to the Registrar-General's statistics, we find some curious features

England and Wales Crude Death rate to a million living

	1940	*1949*	*1958*
Arteriosclerotic heart-disease, including coronary disease (I S C. 420)	573	1093	1863
Myocardial degeneration with arteriosclerosis (I S C. 442 1)	467	617	532
Other myocardial degeneration (I.S C 422 2)	1548	1274	656
Total degenerative heart-disease (I.S C. 420 – 442 1 2	2588	2984	3051

As everyone knows, the death-rate attributed to "arteriosclerotic heart-disease and coronary disease" has increased more than threefold in the past eighteen years, but "myocardial degeneration with arteriosclerosis" has hardly changed at all and "other myocardial degeneration" has fallen to a third, so that if one groups together the rubrics that can be regarded as representing ischæmic heart-disease (I S C 420, 422 1, 422 2), the rate has only increased by a fifth, which is little more than is to be anticipated in view of the increased expectation of life I am, of course, as aware of the defects of comparison of crude death-rates as against standardised mortality ratios, as I am of the answer which John Graunt found to his question, why there were so few deaths attributed to the Pox in the Bills of Mortality Nevertheless, it might be worth while, for those who believe, that by feeding rabbits or men on unnatural diets, they will determine what factors in modern life have caused this spectacular increase in deaths attributed to "coronary disease', to try and find out what are the factors which have caused the almost equally spectacular decrease in deaths attributed to "myocardial degeneration"

When we look at the age-differences, the Registrar-General's tables reveal another curious feature

England and Wales Age differences

	Proportion of Deaths Over 65			*No of Deaths 1958*		
	1940	*1949*	*1958*	*<65 yr*	*65+ yr*	*Total*
All causes	53%	63%	68%			
Arteriosclerotic heart-disease including coronary disease (I S C. 420)	55%	65%	69%	25 962	58,079	84,041
Myocardial degeneration (I.S C. 422)	85%	90%	95%	2195	51 577	53 772

As is to be expected in an ageing population, the proportion of all deaths occurring over 65 is steadily rising, in 1940 it was 53% and in 1958 68%, and the proportions of deaths attributed to arteriosclerotic heart and coronary disease is almost identical (1940 55%, 1958 69%), but of the deaths attributed to myocardial degeneration, 85% occurred at 65 and over, in 1940 and 95% in 1958

Putting this in another way, in 1958 there were 138,000 deaths attributed to "arteriosclerotic heart and coronary disease" and "myocardial degeneration", of which only 20% occurred under the age of 65 Of these 28,000 deaths under 65, 94% were attributed to arteriosclerotic heart and coronary disease, whereas of the 110,000 deaths over 65, 47% were attributed to myocardial degeneration

There are clearly a number of explanations for this difference, but it must be assumed that certifying doctors consider that there is a fatal form of heart-disease which they designate as "myocardial degeneration" or any of the other inclusion terms in rubric 422, which occurs almost exclusively in persons of 65 and over, and accounts for nearly half of the cases of degenerative heart-disease in this higher age-group

Naturally we have no idea what, if any, are the clinical differences or morbid anatomical lesions in cases attributed to these two rubrics but if there are real differences, other than the whims of nomenclature of the certifying doctors, then it would be in keeping with Dr Acheson's[4] observations

Department of Pathology,
Radcliffe Infirmary,
Oxford

A H T ROBB-SMITH

SARCOIDOSIS TREATED WITH CHLOROQUINE

SIR,—I have read with interest Dr Soderstrom's article of Oct 29 in which he described the response of two patients with sarcoidosis to mepacrine He suggested that chloroquine may be used instead of mepacrine

I have treated with chloroquine systemic lupus erythematosus, periarteritis nodosa, Stevens-Johnson syndrome, and other hypersensitivity states since 1953 and rheumatoid arthritis since 1954[5 6]

The ætiology of sarcoidosis is still unproven, but there is a fairly strong suggestion that hypersensitivity may again play a part Michael[7] and Cummings,[8] for instance, related sarcoidosis to the chemical constituents of pine pollen

On the assumption that sarcoidosis represented a hypersensitivity state I have treated two cases with chloroquine since 1957

A married woman, aged 32, was first diagnosed as sarcoidosis, involving mainly the lungs, in 1956 when treatment was started with chloroquine sulphate 200 mg t d s This was continued for six months when it was stopped because of pregnancy By then all lung lesions had cleared Her condition was reviewed in 1957 and 1958, when she was quite well and the X-ray films showed clear lung fields

A married woman of 23 was first seen in July, 1957, when she had characteristic sarcoid lesions on her upper arms, trunk, and buttocks, and hilar-gland enlargement Biopsy confirmed the clinical diagnosis The Mantoux test was negative Chloroquine sulphate 200 mg t d s was started in July, 1957 In September, 1957, the hilar enlargement had greatly diminished and the skin lesions subsided In February, 1959, she was entirely symptomless and stopped chloroquine on her own By May, 1959, there was a recurrence of lesions on the right side of her cheek, upper arms, and buttock Chloroquine was immediately re-started, and by July, 1960, the skin lesions had almost completely disappeared and she felt well This patient is still on 200 mg chloroquine sulphate daily

At the international conference on sarcoidosis in Washington, D C , this year several speakers described the beneficial effect of chloroquine in sarcoidosis

Evaluation of any drug for sarcoidosis is difficult because of the fluctuation in the natural history of the disease with frequent spontaneous remissions This was the reason for not publishing my own limited experience of the drug in sarcoidosis If, however, since it appears that more widespread trials of chloroquine in the management of sarcoidosis are carried out in other parts of the world, then even a very limited trial such as Dr Soderstrom's and my own should be made known It is of particular interest that Dr Soderstrom noted selective staining of sarcoid lesions by the antimalarial There is reason to believe that chloroquine, too, has a selective action on the joints in rheumatoid arthritis, as we have found after 18 months' experience with chloroquine injections into rheumatoid arthritic joints (details are about to be published)

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[4] *ibid* 1960 ii 706
[5] Fuld H *Rheumatism*, 1958 14, 12
[6] Fuld H Horwich L *Brit med J* 1958 ii 1199
[7] Michael M Jr *Ann intern Med* 1956 45 151
[8] Cummings M M Hudgins, P C *Amer J med Sci* 1958, 236 311

Sefton General Hospital,
Liverpool

H FULD

HEATSTROKE

SIR,—I must congratulate you on your editorial of Oct 15 Such is the reputation of your journal, however, that unless I take issue with you on a matter of emphasis it may appear that treatment in a special room with refrigerated water, as described by Guthrie and McCraken,[1] is the best and only satisfactory method of treatment I know that special rooms of this nature are provided in the Persian Gulf—but many a heatstroke has been treated successfully with only the minimum of facilities I feel that it would be better to emphasise the principles of treatment rather than the accessories, which are expensive

At the moment there appear to be two schools of thought on treatment one uses refrigerated water or iced baths or iced sheets and the other artificial sweat and forced air movement I am a convert to the second school ever since I encountered shivering as a response to treatment with iced sheets in a patient who was still hyperpyrexial After this I began to reconsider the physics of reducing body temperature

Everyone knows that during treatment it is important not to reduce the temperature to normal limits as this may give rise to shock, and if shock occurs it is very difficult to treat Immersion in an iced bath can be very "shocking" to even a normal individual just jump naked into the Serpentine next January if you wish to contest this point! Immersion in, or spraying with, refrigerated water coils the body by conduction alone and is associated, sooner or later as the body cools, with peripheral vasoconstriction This vasoconstriction converts the skin, with its superficial fat, into a fairly useful insulating layer

Heatstroke is related to cessation of sweating however caused Evaporation of sweat from the skin, by virtue of the latent heat necessary to effect this, rapidly cools the blood flowing through the dilated skin vessels, which then act as a heat exchanger to the internal organs When sweating has ceased it is logical to provide artificial sweat in the form of tepid water and to aid evaporation with strong air movement In hot climates a powerful fan and tepid water are almost universally available, and it is usually possible soon to accelerate cerebral cooling with an ice bag, or even ice wrapped in a towel, applied to the head

I have no wish to decry the work of anyone who uses refrigerated water or iced baths, because I feel that in their experienced hands this form of treatment is both successful and safe To the average doctor, however, heatstroke is a comparatively uncommon emergency and treatment must be given at once with facilities readily available I can assure you that it is perfectly possible to treat successfully hyperpyrexia of any ætiology by sponging with *tepid water and a strong air blast from a fan, even in* conditions of high relative humidity and high ambient temperature

R.A F Institute of Pathology and
Tropical Medicine,
Halton Aylesbury Bucks

R MORTIMER

SIR,—Your leader is very valuable Hyperthermia (as we used to call it) will follow the treatment of patients with malaria, sandfly fever, enteric fever, and influenza in uncooled hospital wards Cardiac failure is uncommon in hyperthermia, except when the condition has persisted untreated for some hours

Servicemen have been known to report sick, with pyrexia, and been sent back to their quarters, and found hyperthermic and unconscious some hours later, in such cases cardiac failure is not uncommon and the response to the most enlightened treatment is disappointing

As you say, proper application of the principles of prevention, which are well known, should be everywhere applied, especially in Service communities, and devices for effective cooling should be at hand in all situations where heatstroke is known to occur I emphasised this in 1937 [1]

St Margaret's Hospital,
Epping

FRANK MARSH

SPONTANEOUS FRACTURE OF THE FIBULA

SIR,—Dr Hobbs (Oct 22) raises an interesting point when he states that in fatigue fractures of the fibula no adequate explanation of their occurrence has been given

These fractures occur in two main groups (1) the young and athletic and (2) the middle-aged and tired The case described clearly is of the second type Fatigue in bone may be compared in some respects to that in other materials such as metal When a metal column is subjected to repeated eccentric loadings, alternating tensile and compressive strains occur and eventually lead to a fatigue or stress fracture This also happens experimentally in bone Gaynor Evans [2] reported on subjecting a piece of fibula to repeated cyclical loadings at 5000 lb per square inch, and after 3,000,000 such loadings fatigue fractures occurred

In life, however, bone has a built-in capacity to repair by osteoblastic action and only when the stimuli are repeated sufficiently within the time taken to repair is a fatigue fracture liable to occur This period is likely to be prolonged in the middle-aged Even then, if aching causes the activity to cease, the early fracture may pass unrecognised

Windsor

ROY MAUDSLEY

POLIOVIRUS-NEUTRALISING ANTIBODIES IN STOOLS

SIR,—Dr Godtfredsen's letter of Aug 13 reported failure to demonstrate poliovirus-neutralising antibody in the stools of 13 convalescent individuals We appreciate being informed of these results and hope that she and others will not cease efforts to determine the nature of resistance of the human alimentary tract to poliovirus following infection with wild polioviruses or the feeding of attenuated living poliovirus vaccines Such alimentary resistance does not accompany Salk vaccination

Our communication [3] reported the demonstration of specific antibody in the stools of 13 children recovering from poliomyelitis Actually this represented only the positive results, the tests were performed in 93 convalescing patients and *only* 13 individuals were positive Once a given stool is demonstrated to contain type-specific poliovirus antibody, the observation can be repeated and appreciable loss of titre through storage and re-thawing has not been observed The serotype of antibody observed in our 13 positive children were 5 for type 1, 3 for type 2, 4 for type 3 One child's specimens neutralised types 1 and 2 When antibody was found in the stools the same type (and of course one or both remaining types) of antibody was found in the serum As we pointed out, the stool antibody when found was always *heterotypic* to the infecting virus, suggesting that those individuals' alimentary tracts had had previous exposure(s) to poliovirus

Deviations in Dr Godtfredsen's technique from ours include our use of a suspended-cell technique, which has advantages in demonstrating "low-avidity" antibody, and our use of 0 25 ml of the stools tested instead of 0 1 ml

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[1] Guthrie J, McCraken, A V *Lancet*, 1960, i, 682

[1] British Encyclopædia of Medical Practice vol vi, p 396 London 1937
[2] Gaynor Evans, F Stress and Strain in Bone Springfield, Ill, 1957
[3] *Lancet* 1959, ii, 272

Whether the test details per se are important is uncertain, but more children may need testing our record of 13 of 93 individuals (± 14%) suggests this Failure to demonstrate in vitro neutralising antibody of the usual kind in the stools of the remaining 80 patients may be purely technical or may have fundamental explanations The age of patient, time of stool-collections after the current infection, previous alimentary contact with the other serotypes of poliovirus, the " secretor " status of the patient's alimentary tract, and other factors may influence the results

Ascertaining the modus by which the alimentary tract resists infection after experience with live virus but not following intramuscular vaccination is important from the epidemiological, clinical, and general biological points of view It is hoped that studies of this kind with varying approaches in technique will be conducted by as many workers as can interest themselves in this field

University of Louisville, Kentucky

ALEX J STEIGMAN
MURRAY M LIPTON

STERILISATION OF THE DIABETIC'S SYRINGE

SIR,—The recent correspondence on this subject recommends several methods to be safe and trouble-free

On the one hand, Dr Wauchope (Sept 10) doubted whether sterilisation was necessary and described her fortunate personal experience without any infections for many years But I fear that many insulin patients would have less high standards of cleanliness than hers and this is a very important point not mentioned in the previous correspondence How well I remember a young woman who, after five years of trouble-free injections, developed mysterious abscesses on both thighs The bath she received on admission to hospital for investigation stopped all further troubles, and she told me that she had moved to a house where there was no bath and this explained her abscesses

What do the insulin manufacturers say in their insulin packages? Nothing very definite. Most of them say that boiling in tap-water is desirable but as that is not always possible, advocate keeping the syringe and needles in spirit

The balance of the advice given by your correspondents is to favour spirit alone, although the initiator of the correspondence, Dr Stephen Carter, boils his syringe four times a year and uses no spirit

London, W 1

R D LAWRENCE

SUICIDE

SIR,—Reading Dr Stewart's article of Oct 22 it is difficult not to feel compassion for many of the 85 suicides in his series of 122 who had been suffering from various painful or disabling diseases

Is it not time that the coroner's court formulæ, " while the balance of his mind was disturbed " or " while of unsound mind ", should be discarded in the absence of clear evidence of mental disturbance prior to suicide? Some people who commit suicide to terminate a life that has become a life-sentence of intractable pain are taking a step that seems sensible albeit desperate

As you report last week (p 976), a Bill to provide that suicide and attempted suicide should no longer be criminal offences has been drawn up and approved by the Criminal Law Revision Committee So need we penalise the suicide by casting an unmerited slur on his sanity just because he has committed suicide?

With regard to attempted suicide, Prof E Stengel[1] has for a long time taught that one of its main motivations is the appeal of a desperate individual for help from his fellow-men Unless the family or friends of the attempted suicide are alerted to his dangerous dilemma by the suicidal attempt, the only practical step likely to prevent a second, possibly successful, attempt would seem to be bringing him before the courts and placing him on probation on condition that he receives necessary psychiatric treatment It is to be hoped that this potentially lifesaving course will not be made more difficult if the new Bill becomes law

London, W 1

F R C CASSON

THE NATURE OF ESSENTIAL HYPERTENSION

SIR,—I really must take exception to the data which Dr Marshall (Oct 22) alleges add to the solution of this problem, and the conclusions he draws from these data

My old chief, Sir Thomas Lewis, would not allow readings of blood-pressure taken by nurses to appear in scientific publications The estimations which Dr Marshall uses were made by " specially trained nurses at hourly intervals during one day a patient spent in hospital " They were made to the nearest even number Dr Marshall states that digit preference can be excluded because the nurses had no incentive Nor had those employed by Boe, Humerfelt, and Wedervang[1] in their measurements made on 67,976 inhabitants of Bergen Yet digit preference was more marked than in any other series I know 85% of systolic readings (series I) ended with 0 and only 15% with 5 For diastolic readings the percentages were 87 and 13 respectively Diastolic pressures had a bimodal distribution in the second but not in the first sample This bimodality was most probably due to a change in the team of nurses making the measurements There is no analysis in Dr Marshall's paper of the distribution of readings, nor any evidence that steps were taken to assess how accurate the readings were

As disturbing is his statement " Moreover, the blood-pressure figures used in this study were means of six readings taken under constant conditions " To those who work in the field of science, " constant conditions " has a clear implication, and is a state, in fact, very rarely achieved Dr Marshall's 134 patients " attended hospital for one day during which they rested on a bed in the supine position Their blood-pressure was recorded hourly for six hours by specially trained nurses, who read the sphygmomanometer to the nearest even number " One could perhaps imagine that from 10 to 4 the patients lay on a bed in a side-ward and were visited only by the nurses But this was not so " During the one day in hospital the patients had a physical examination, chemical and microscopic examinations of the urine, estimation of the blood-urea and blood-cholesterol, an electrocardiogram, and a radiographic examination of the heart and skull "

Dr Marshall's averages of six values, each to the nearest even number, will give him a series of integers which perhaps he might take to one place of decimals As set out they are arranged in groups at intervals of 8 or 12 mm Hg He does not say how this grouping has been done And yet it is vital to the conclusion the reader is invited to accept

However, the worst feature of Dr Marshall's paper is his evidence for bimodality A protest has been made before against interpreting irregularities in frequency distribution curves as bimodality, especially when the numbers are small Fortunately Dr Marshall has now brought this practice to what must be the all-time low

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[1] *Lancet* 1952, i, 1059

[1] Boe J, Humerfelt S, Wedervang, F *Acta med scand* 1957 suppl 321

He says " The systolic pressures of patients over 60 years had a bimodal distribution irrespective of whether their parents died below or above the age of 65 (fig 5) " Fig 5 shows the frequency distribution curve of 26 patients whose parents had died under the age of 65 Here are data taken from fig 5 for this group

Systolic B P	*Frequency %*	*Actual number*
108	4	1
120	12	3
132	4	1
144	8	2
156	12	3
168	24	6
180	16	4
192	8	2
204	12	3
Total	100	25

The contention evidently is that a series 1 3 1 2 3 demonstrates bimodality

Finally, supposing that an analysis of patients between the ages of 31 and 70 showed that there were essentially two populations as regards blood-pressure—and has this not been shown by Dr Marshall ?—could this be accepted as evidence that essential hypertension is the manifestation of a single gene ? For Dr Marshall states " It seems likely that the appearance of a group with raised blood-pressure is caused by a hereditary factor—probably, as Platt suggested, due to a mendelian dominant " It should be clearly stated that cerebral vascular disease consists of at least three entities occlusion of the arteries in the neck, of those within the cranium, and cerebral hæmorrhage There is a strong suspicion that the last is more closely associated with grossly raised pressure than the first of these Dr Marshall says that these patients had " what was judged on clinical grounds to have been a non-embolic cerebral infarction ", but, as previously reported,[2] his trial of anticoagulant treatment had to be stopped because of the incidence of fatal cerebrovascular accidents due to cerebral hæmorrhage in the treated group Had he indeed demonstrated two populations in cases of cerebrovascular disease this would have no bearing whatsoever on whether essential hypertension is or is not the manifestation of a single gene

Oxford G W PICKERING

SIR,—Before some of your readers should be tempted to interpret the results found by Dr Marshall as cogent evidence in the conflict of views on the nature of essential hypertension, could we have the answers to some simple questions ?

(1) We are told that the subjects studied had all previously had what was judged to have been a non-embolic cerebral infarction In what ways were these survivors thought to be representative of all people suffering cerebral infarction, how were the subjects selected, and why were there 91 males and only 43 females when mortality-rates from vascular lesions involving the central nervous system show no gross sex difference

(2) Having demonstrated such very different frequency distributions of arterial pressure in the two sexes as those shown in fig 1 (*b*) and (*c*), what is the justification for combining the two sexes in all subsequent analyses ?

(3) In analysing blood-pressure data for subjects aged 31-70 is it reasonable to use only two age-groups, above and below 60, when the evidence derived from the general population shows arterial pressure to be very sensitive to age ?

(4) The grouping of pressure into units of 12 mm Hg for systolic and 8 mm for diastolic pressure is unusual Could this have influenced the shape of the published curves ?

The type of study carried out by Dr Marshall could
be repeated in many hospitals in the country but
have little value unless confirmed in less highly s
populations Before we are confused by more and
bimodal curves, may I make a plea, Sir, that a
should publish their data in a form that enables int
readers to evaluate them and allows comparison with
published work, and particularly with the careful v
Platt and Pickering Pictures alone are unsatisfac

Llandough Hospital,
Penarth, Glamorgan W E Mi

SIR,—There seems to be a growing and unfor
tendency, especially in communications on hypert
to argue from diagrams The latest example is the
of Dr Marshall, who relies upon them entirely an
no figures at all It must be admitted, however, t
sin is a minor one, for as his numbers are very sm
corresponding frequencies can be reconstructed
almost complete accuracy from his curves shown
centages Nevertheless, one would like to have th
data in less coarsely grouped form And, incide
how can pressures measured to the nearest even n
be added so as to yield the series of figures sho
group centres in all the diagrams ?

The following opening paragraph has appea
chapter II in all successive editions of R A F
Statistical Methods for Research Workers, right back
first edition of thirty-five years ago

> " The preliminary examination of most data is facilitated
> use of diagrams Diagrams prove nothing, but bring outs
> features readily to the eye, they are therefore no substitute
> critical tests as may be applied to the data, but are valu
> suggesting such tests, and in explaining the conclusions
> upon them '

The current discussion on the nature of es
hypertension will be greatly helped if these wise wor
remembered, and if authors give as much of their
data as possible, apply suitable tests, and in par
explain just what they have done, desiderata stri
lacking in some recent papers The curves can ther
their proper purpose of illustration and light relief

M R C Clinical Genetics Research Unit,
London, W C 1 J A FRASER ROBE

SIR,—It has been pointed out to us that we
wrong (Oct 15) in saying of Miall and Oldham's
that there were only 24 subjects with diastolic pre
" greater than 100 mm Hg " This should hav
" 105 mm Hg and greater ", &c We are very sor

S L MORRI
J N MORRIS
London, E 1

CYCLICAL ŒDEMA AND SHOCK

SIR,—I read with great interest your leading arti
Oct 1 You mentioned that apparently the urine w
tested for hydroxyindole-acetic acid in the patie
described [2]

In the interest of completeness, I should like to ad
although we did not include this in the published r
the 24-hour urinary excretion of 5-hydroxyindole
acid was measured on 5 occasions in this patient, incl
during a shock phase, during a recovery phase, and
a time when she was asymptomatic These determin
were performed by Dr O Dhodanand Kowles
New York Hospital The values were all between
3 mg per 24 hours (normal up to 8 mg per 24 hou

New York. BAYARD CLARKS

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[2] Marshall J Pathogenesis and Treatment of Occlusive Arterial Disease p 99 London, 1960

[1] *Clin Sci* 1958, 17 409
[2] *Amer J med* 1960, 29 193

MODERN CLINICAL BIOCHEMISTRY

R,—I would not put the clock back 50 years as Dr dry forbids (Oct 29), but 113 years and quote from how's paper, Standpoints in Scientific Medicine can learn much from chemistry, but we will have to ve for ourselves the privilege of applying its findings" how was familiar with the appreciable number who e Dr Hendry's outlook in his 1855 paper on Cellular ology he writes "The condescension with which the onents of chemical and physical viewpoints—even e who have only a very imperfect understanding of oscopic anatomy—look down on morphology is known"

om my student days I have had the highest regard for d we receive from competent biochemists if they their right place in the team they are invaluable I ngly dislike splitting the pathology department into or more watertight compartments Whenever I look n my microscope problems in bacteriology, hæmato-y, or biochemistry arise, with the aid of one or other mber of my team these are followed to the advantage of clinician and patient Our biochemist regularly draws attention to problems which should be followed in er departments Without a medical training very few chemists are safe in advising on the meaning of many their findings A good example of the interdependence the four departments of the pathological laboratory was man of 23 admitted to one of our surgical wards in a ate of diabetic coma When the biochemist told me of s very high blood-sugar I at once asked why he was in a urgical ward it was because he had had a bladder-neck peration for enuresis there three months before I dis-overed that he was not then a diabetic, so we at once amined his blood for severity of infection (if any), and is urine for pus and organisms The real diagnosis was uickly established as pyonephrosis, and unfortunately roved at necropsy To me all sections of the laboratory e equally important in general Who is the most impor-nt departmental head varies with the case, for the young an just mentioned I would say it was the hæmatologist ecause he said clearly death from infection is inevitable the absence of successful treatment

The question of who is the most important, the patho-gist or one or other of the technical heads of departments, an absurd one It is well answered by Leo Tolstoy in s short story Three Questions written in 1903 (in *wenty-Three Tales*) I hope Dr Hendry and others who ink like him will read this The practical point is that pathologist is usually the only one who can bring all ctions of the laboratory to the aid of the clinician, he ove all others can cheat death when he calls too soon he greatest emotional satisfaction is to be found in neral practice, the greatest intellectual satisfaction in the ological department The former is warm, the latter o often cold, that is why many of us feel like Dr Hendry t times If this emotional satisfaction is wanted, do not ecome a physician or surgeon as Professor Cappell ossibly suggests, for they occupy a half-way position, btain a medical qualification and enter general practice

Dr Hendry may be shocked to know that to me the biochemist ranks equally with the senior technician in harge of hæmatology, bacteriology, and histology I do not know which is the most important until I know the blem If the training of a biochemist is more difficult, d all will not agree with this, they should be paid re—as they are This makes a psychological barrier een them and the technical heads of the other departments which a wise biochemist will do all in his power to destroy

Biochemists are not at the crossroads looking four ways at once at the moment they are looking on the way out only If that happens it will be a tragedy We do not have far to look to see non-medical biochemists who are invaluable in the practice of medicine, they are professors or of that calibre This is taken to mean, by some, that all we need to do to obtain a good biochemical service is to appoint a good chemist in charge of it and then keep away This is nonsense My biochemistry department owes a lot to men with medical qualifications, these are ideal but in short supply Even Dr Hendry might allow that the greatest clinical biochemist of all time was the medically qualified Paul Ehrlich

How should the pathological services of the future be planned? Division into a number of watertight compartments is an evil which may be necessary in places The right thing seems to me a large general clinical laboratory where a problem in a patient is studied, not just a test performed This should be backed by small reference laboratories in the same building Most of the routine biochemistry should be done in the clinical laboratory—including the blood sugars and ureas for which Dr Hendry has such contempt, though if I could have only two biochemical investigations I would pick these

How should junior and senior members of the medical profession use the pathological services? I give two answers to this Because so many tests are needed the pathologist can no longer attend to all Many are straightforward and the patient progresses well, these cases justify a request for a given test Many patients are diagnostic problems or are unsatisfactory If a patient is, say, unsatisfactory after an abdominal operation I like the surgeon to tell me what he did and invite our help At the moment many are obsessed with biochemistry to the exclusion of the other branches The correct use of all departments will invariably say peritonitis, ileus, both or neither We want to know the process, not some minute detail of it When we begin our training with the microscope we use the highest magnification we can get, and feel that if we could only obtain something larger we would know everything As we become more experienced we use the lowest magnification so that we can see the process This earns us scorn from the most junior my son, when a dental student, assured me that I only guessed at such a low magnification I fancy that many, who should know better, feel that in biochemistry they have something of higher magnification than the electron microscope Perhaps they have, but the sap in a leaf tells you little about the plant and less about the forest.

May biochemists read Leo Tolstoy and remain our honoured colleagues May I be permitted to salute Professor Cappell's masterly survey

Derbyshire Royal Infirmary,
Derby

G R OSBORN

SIR,—There is an element of truth in Dr Hendry's statements about the interrelationship of "pathologist" and biochemists, but surely many will think he overstates his case, and confuses any serious analysis of the position, both by his caustic wit and blatant misuse of the names of the reactants It is patently absurd to imply that each large hospital should have an autonomous biochemistry department such a separist movement would be harmful to the patient and the clinician, and more particularly to

the biochemist himself What is clearly needed is a greater integration of the laboratory services, both within their own house and within the framework of the hospital as a whole No hospital worker, be he physician, surgeon, histologist, or biochemist, can go it alone, even if the latter thinks he can do it all himself It is, of course, platitudinous to say there is no place for the enthusiastic amateur in this modern scientific work, each specialist must overtly be trained as such, but he would be a fool indeed to suppose he alone has something to offer the patient, whatever the latter's disease

Pathology is the study of disease however Dr Hendry may interpret biochemistry to himself, in clinical practice it is the application of chemistry to the study of human disease, and it must follow that even he is to some extent a pathologist I personally would like the terms pathologist and pathology laboratory, as currently used, to be discontinued, in hospitals at least Instead, the terms bacteriologist, biochemist, biophysicist, hæmatologist, histologist, or virologist could be used according to taste each worker should have an individual laboratory, but all should be contiguous and in one central building, so having common meeting and stamping grounds Medicine and pathology have both suffered enough enthusiastic divisionists already without further chemical schizists

County Hospital,
Lincoln

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HYDROCORTISONE AND CORTICOTROPHIN IN HERPES ZOSTER

Sir,—During the past three months I have been using short courses of intensive hydrocortisone 10 mg t i d for four days in severe cases of herpes zoster—with dramatic results

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Epidemiological studies such as those commented on in your editorial have produced substantial results Such studies may, however, prove even more rewarding in th future when epidemiological techniques are correl with the more precise laboratory techniques of th modern medical virologist

School of Hygiene,
University of Toronto

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A few weeks after my first case our registrar encountered this mishap, and deflation of the cuff again reversed a potentially serious position

Morriston Hospital,
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J M Lewis

HAZARDS OF BARIUM-SULPHATE ENEMA

Sir,—Your annotation of Oct 8 refers to barium sulphate pulmonary embolism The following case may therefore be of interest as a record of a further hazard in relation to this common diagnostic procedure

A fit man of 70 was referred from the outpatient department for barium enema He complained of mucous diarrhœa Technically the enema was uneventful On walking from the X-ray table he complained of sudden severe abdominal pain and collapsed to the floor The radiologist reported that he was unconscious for some seconds He was transferred immediately to a general medical ward

When examined he was conscious, complaining of generalised abdominal pain and mentioned a transient sharp left-sided chest pain No peripheral pulses were detectable, blood pressure was unrecordable and the jugular venous pressure was raised It was then observed that a striking generalised erythema was developing it reached a maximum some 45 minutes after completion of the enema, and faded gradually over the next 6 hours

Immediate resuscitation was symptomatic, using oxygen, *morphine, intravenous pressor agents, and intramuscular* promethazine Chest X-ray, plain X-ray of the abdomen, electrocardiogram, serum-transaminases, and urinary 5-hydroxyindole-acetic acid were all subsequently shown to be normal The barium enema showed a few diverticula in the sigmoid colon but no other abnormality The patient made an uneventful recovery and was discharged 10 days later The cause of his abdominal pain remains obscure

In view of the negative findings and the clinical picture, this man may have had an acute hypersensitivity reaction The barium enema was made up in 1% tannic acid and was preceded by colonic irrigation with tap-water followed by 'Veripaque' enema A similar investigation 4 months previously with the same preparation was entirely uneventful Skin tests using 1% tannic acid were negative

Fatal collapse due to proven barium-sulphate pulmonary embolism has now been reported [1] A second case in which this diagnosis seems highly probable, although necropsy was not allowed, has recently been recorded [2] Acute "water intoxication" in the preparation of children for barium enema is now a well-recognised and sometimes fatal hazard [3–5] But the condition I have described does not seem to have been recorded previously

Over 1000 barium enemas are performed annually in this hospital, no member of the staff of the department of radiology has seen or heard of a similar case Although,

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I should like to thank Dr G D Hadley for his advice and perssion to publish this case

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Memorial Hospital of Long Beach,
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GEORGE X TRIMBLE

ORAL TREATMENT OF PERNICIOUS ANÆMIA WITH LOW DOSES OF H P P /1

SIR,—Dr Varadi (Oct 15) must realise how increasingly ifficult it has now become for us to assess the significance f his findings, faced as we are with three differing escriptions of the treatment given, and the responses btained, from the same ten cases It is also a matter of ome surprise to find that he classifies a case as " relapsed " Sept 17) when, in fact, the patient did not suffer a eterioration in the blood-picture at all, but merely a fall n the serum-B_{12} level when the daily dose was reduced rom 300 μg to 100 μg of B_{12}

Finally, it is a little disappointing that Dr Varadi has till declined to explain the scientific basis of his interretation of serum-B_{12} levels, when applied to this articular form of therapy We do not doubt that the stimation may be of some value in confirming a diagnosis n the untreated case of pernicious anæmia, but we would ike to know what evidence he has for the conclusion in the enultimate paragraph of his letter of Sept 17, that erum-B_{12} levels also reflect the degree of intestinal bsorption, *on this particular form of therapy*

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SIR,—Like Dr Varadi and Mr Elwis (Sept 17) I have been investigating the serum-vitamin-B_{12} levels of patients with pernicious anæmia in relapse who have been treated with vitamin-B_{12}/peptide (' Distivit ')

In 8 such patients receiving 200 μg daily or less, followed for periods of three to eighteen months, the serum-B_{12} concentration rose above 200 μμg per ml in 1 case only A further 2 patients given 500 μg daily for a period of eighteen months maintained serum levels around 400 μμg per ml These results are broadly similar to those previously reported [4] using oral crystalline vitamin B_1 With the exception of 1 patient receiving 100 μg daily, all these cases reached and maintained normal values of hæmoglobin, red-cell counts, and packed-cell volumes, so Dr Mooney and Dr Heathcote (Oct 1) could again, on this evidence alone, question the scientific basis for using serum-vitamin-B_{12} levels as proof of adequate dosage I submit however that, as a general concept of rational therapy, it is desirable to give a sufficient amount of the vitamin to maintain the serum level near the average normal mean—that is, about 400 μμg per ml It therefore seems necessary, if oral treatment for pernicious anæmia is considered desirable for a particular patient, that over 200 μg daily should be administered, whether the vitamin B_{12} is in a crystalline form or a peptide complex

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(*a*) The G P s agreed unanimously that their medical-school training had not fitted them for their work, (*b*) that, with few exceptions, hospital doctors who had trained them had little knowledge or understanding of the problems facing the G P , (*c*) that, despite a growing awareness of these deficiencies in training, the situation has not improved of recent years

In a laudable attempt to correct an unbalanced system of training, some universities and the College of General Practitioners have introduced schemes to allow medical students to see something of general practice during their training Apart from local schemes which allow students to spend a few weeks with selected G P s, there are the Edinburgh and Manchester University schemes On a more ambitious scale the Inverness Regional Hospital Board is providing rotating internships, which include attachment to G P s, and the Wessex scheme financed by one of the Nuffield Trusts is seeking to provide young G P s with a chance to see something of all three branches of the Service

No-one would wish to minimise these efforts Yet surely they leave the main problem unsolved The hospital teacher who will continue to form the minds of new generations of students is still out of touch with the problem of general practice How can this be otherwise when the career structure in the hospital field demands that the young trainee consultant should unremittingly follow the narrow lines of his specialty ?

I suggested at our conference that the problem could be partly solved if every future teacher in the hospital service had to spend a period in general practice—a proposal which was warmly welcomed The time to do so would be between the registrar and senior-registrar appointments—i e , before the young specialist sets his foot on the ladder from which he dare not fall off If the time spent in general practice were made a condition of appointment to a senior-registrar post, no-one would gain an unfair advantage

Unlike the G P trainees, these young aspiring specialists would not have to be taught general practice by selected good G P s Their need is to see the realities of practice in all its forms They could be attached to four different types of practice for six weeks each, and could learn quickly some of the problems facing the industrial, semi-urban, rural, and seaside G P In all, this would occupy only six months of their working lives, yet it could have a profound and beneficial effect on the future training of the medical student—and, indeed, on British medicine

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Obituary

ALAN BROWN

M D Toronto, F R C P (C), F R C P

Dr Alan Brown was one of the pioneers of pædiatrics in Canada For over thirty years he was physician-in-chief to the Hospital for Sick Children in Toronto, and when a chair of pædiatrics was set up in the University of Toronto in 1935 he was appointed the first professor He died on Sept 7 at the age of 73

He qualified from the University of Toronto in 1909, and spent five years as a resident physician in the Babies' Hospital (Columbia University), New York After further postgraduate study in Germany, Austria, Denmark, and Britain, he was appointed to the medical staff of the Hospital for Sick Children in Toronto in 1915 Four years later he became its physician-in-chief Under his direction the hospital became a centre for the training of medical undergraduates, pædiatricians, and nurses In 1919 he was appointed an associate professor of medicine in the university, and in 1935 head of the newly created department of pædiatrics He served for many years as consultant to the local, provincial, and national departments of health, as well as to three other Toronto hospitals and the former Infants' Home He was a founder and past president of the Canadian Pædiatric Society He retired from his hospital appointments and his chair in 1951

As a writer and a visitor he was well known on both sides of the Atlantic His book on *The Normal Child*, first published in 1926, is now in its fifth edition, and with Dr F F Tisdall he published a useful survey of *Common Procedures in the Practice of Pædiatrics* He gave many clinical lectures, and his colleagues in this country will recall his Ingleby lectures in 1948 on the scientific construction of the normal child's diet He was a corresponding member of the British Pædiatric Society and was elected F R C P in 1940

E C R writes

"Alan Brown crusaded vigorously for many improvements in the care of infants and children, including the proper formulation and sterilisation of infant feedings, the compulsory pasteurisation of milk, and the universal use of diphtheria toxoid and other well-established immunisation procedures Soon after he became physician-in-chief, he organised a small research laboratory at the hospital which, with his support and encouragement, has grown greatly with the years in both size and reputation Canadian pædiatrics in general and the Hospital for Sick Children in particular owe a great deal to his vision, unusual energy, and outstanding organising ability "

Dr Brown married Miss Constance Hobbs in 1914 She survives him with their two daughters

CLAUDE WILFRED ALFRED KIMBELL

M B N Z , F R C O G , F R C S E

Mr Claude Kimbell, gynæcological surgeon to the Samaritan Hospital for Women, London, died on Oct 26 at the age of 55

A New Zealander by birth, he was educated at Wellington College and the University of Otago, where he graduated M B in 1930 The following year he came to this country for postgraduate studies, and in 1935 he took the F R C S E and in 1937 the M R C O G During the late war he served in the R.A M C with the rank of major He remained behind at Dunkirk to look after the wounded and spent the rest of the war as a prisoner in Germany Afterwards he returned to practise obstetrics and gynæcology in London and was appointed to the staff of the Samaritan Hospital and the City of London Maternity Hospital He was elected F R C O G in 1953 He was a founder member of the Gynæcological Travellers' Club

C M G , one of his colleagues at the Samaritan Hospital, writes

"Claude Kimbell was a sick man for many years, but because of his courage and interest in life he continued with his work In the Samaritan Hospital he was loved by everyone he worked with in the outpatient department, wards, and theatre. An excellent surgeon, he was interested in the total human and always concerned with the psychological implications of a case He was a perfectionist and ever ready to sacrifice himself for his patients and friends From his experience as a prisoner-of war he had learned not bitterness but a deep sympathy and understanding of his fellows "

J H , who first met Kimbell twenty-five years ago on visits to Liverpool when Kimbell stayed with his fellow New Zealander, the late Charles Marshall, came to admire "his many qualities as friend and surgeon" He relates

"Knowing that his health was failing Kimbell lately made a trip to Canada as a ship's surgeon to see his married daughter and grandchildren In a Newfoundland hospital he found a sailor who had been seriously injured four months previously No one would take the responsibility to send the sailor back to England and his family It was typical of Claude Kimbell that he organised a passage home on his own ship for this injured man, and on arrival in Liverpool with great energy arranged for him to be sent home to his family

"As a surgeon Kimbell was meticulous in detail and deft in technique As a man I can sum him up in four words—modest, honest, generous, and always considerate of others "

Public Health

The Registrar General's Commentary

IN his commentary on the vital statistics for 1958 the Registrar General[1] notes that the birth-rate of 16 4 per 1000 was the highest recorded since 1949 There were 740,715 live births, the largest number since 1948 The birth-rate per 1000 women aged 15–44 was 82 1 in 1958, which was above the level of the early 1920s and 32% higher than the 1938 rate The birth-rate was highest in Merseyside and lowest in Greater London

Population —The annual rate of increase amounted to about 0 5% of the population, a little less than the average rate of population increase for Northern and Western Europe, and only a third of the rate of increase in Asia The estimated total population at mid-1958 was 45,244,000 (21,877,000 were males and 23,367,000 females)

Marriages —In the 15–24 age-group, the proportion married has more than doubled since 1931 for both men and women Although total marriages were 7000 less than in 1957, the rates continued to rise slightly at the younger ages In 1954, 6 9% of bridegrooms and 28 6% of brides were minors, the corresponding figures for 1958 were 10 7% of bridegrooms and 35% of brides

Deaths —The crude death-rate—11 7 per 1000 persons of all ages—showed little change With allowance for population age-changes, the average reduction in mortality has been 60% in the past fifty years, and 40% in the past twenty-five years Between 15 and 24 years, the death-rate for males is more than double that for females, in this age-group seven times as many men as women die from accidents

Infant mortality —This continued to decrease deaths of children under 1 year numbered 22 5 per 1000 births in 1958, the lowest rate recorded till then Infant mortality as a whole has declined by two-thirds since 1928

Tuberculosis —There were 4480 deaths in 1958, compared with 19,797 in 1949 In the same time, annual notifications have declined from over 50,000 to 30,000

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[1] Registrar General's Statistical Review of England and Wales, 1958 Part III, Commentary H.M Stationery Office Pp 222 13s

Accidental and violent deaths.—These have increased progressively, the totals being 18,513 in 1949 and 22,456 in 1958. The increase is due mostly to increases in motor-vehicle accidents, accidental gas-poisoning, falls, and, in women only, suicide. The death-rate among men in the 15-24 age-group from motor-vehicle accidents increased from 26 per 100,000 population in 1954 to 35 in 1958. Accidental deaths attributed to barbiturate poisoning increased from 77 in 1949 to 205 in 1958, and to domestic gas from 421 to 870.

The September Quarter

In England and Wales in the September quarter, 1960, there were 197,572 live births, 3873 stillbirths, and 112,379 deaths.[1] The birth-rate (17.2 per 1000 population) was the highest for a September quarter since 1948, when the corresponding rate was 17.5. The stillbirth-rate was low—19.2 per 1000 live and still births.

Parliament

Professions Supplementary to Medicine Bill

THIS Bill received the Royal Assent on Oct. 27. Its provisions will not come into operation until they are brought into force by Orders in Council.

QUESTION TIME

Hospital Casualty Services

Earl WINTERTON asked the Government whether, in view of the criticisms made by an unofficial committee of the methods for dealing with casualty cases in National Health Service hospitals and of other evidence to the same effect, they would appoint a committee of inquiry.—Lord ST. OSWALD replied: My Lords, the Standing Medical Advisory Committee of the Central Health Services Council appointed, earlier this year, a subcommittee, under the chairmanship of Sir Harry Platt, to consider the organisation of hospital casualty and accident services and to make recommendations regarding their future development. The Scottish Health Services Council has set up a similar committee. I have no doubt that these committees will consider the recommendations made in the study, based on 20 casualty departments, which was recently published for the Nuffield Provincial Hospitals Trust.

Lord STONHAM: Is the noble Lord aware that, at the instance of the Minister, every regional board has been considering this problem, that they are proposing to concentrate major casualty centres in the hospitals in each group, but that what is needed is more money to equip, expand, and provide more casualty centres? And can he say whether that will be forthcoming?—Lord ST. OSWALD: I think that any decisions of that nature must naturally rest upon the finding of this subcommittee, which has been set up specifically for the purpose of discovering what the facts are, and of suggesting remedies.

Means Test for State Scholarships

Mrs EIRENE WHITE asked the Minister of Education what decision had been reached on the recommendations of the Anderson Committee on parental means tests for university students.—Sir DAVID ECCLES replied: I shall very shortly announce a radical revision of the present means test, to be brought in by the autumn of 1961. This is without prejudice to the abolition of the means test if that, on full examination, should turn out to be required.

Smokeless Zones

On Oct. 1 there were 296 smokeless zones or smoke-control orders in operation in England and Wales, covering 255,974 premises, and 98 more smoke-control orders, covering 123,219 premises, have been confirmed but were not in operation. Some 1270 local authorities have not made smoke control orders, but most of these do not have a major problem of domestic smoke pollution.

Notes and News

WORLD HEALTH ORGANISATION

THE Director-General of W.H.O., Dr M. G. Candau, and the retiring senior W.H.O. representative in the Congo, Dr J. S. MacKenzie Pollock, have both reported on the medical situation there.

In July W.H.O. responded to a request by the Security Council, and within a week 28 staff members had been sent to the Congo. 28 medical teams provided by 25 national Red Cross societies answered a joint appeal by the League of Red Cross Societies and the International Committee of the Red Cross. These teams were initially to stay three months. Some countries offered additional assistance, and soon hospitals, not only in the cities, but in the country as well, were able to function again.

At each provincial capital, except that of Katanga, there is a W.H.O. group, consisting of a public-health adviser, a public-health engineer, and a mobile epidemiological team. These mobile teams have already begun to organise vaccination campaigns against smallpox, typhoid fever, yellow fever, and plague. To deal with these diseases and the other major health hazards—malaria, filariasis, leprosy, and tuberculosis—many staff members are being recruited. They will be paid out of the U.N. Congo fund and placed at the disposal of the Congo Government. The main need is to staff the district services with doctors who will superintend the hospitals and organise preventive health services. 130 health personnel are being recruited now, and this number will soon be increased to about 500. The Red Cross teams have been asked to remain for six months, or longer if possible.

The long-term problems can be solved only by training Congolese doctors. There are none at present, and the local university, Lovanium, will graduate only 2 in 1961, and not more than 19 in all by 1965. Dr Candau considers that the 1959 situation cannot be regained in less than twelve to fifteen years. But an encouraging start has been made. W.H.O. is providing 13 additional teaching staff, including the first professor of public health, which has enabled Lovanium University to increase its medical-student intake to 40. The three schools for "medical assistants" will finish the six-year training of the present students and then close. All students after that will complete the full medical course at Lovanium University. 74 "medical assistants" are at present helping to provide essential health services.

Meanwhile 60 "medical assistants" have been awarded W.H.O. fellowships and have left for French medical schools to qualify as doctors after special two-year or three-year courses. 7 students with no previous training have been awarded fellowships for a full medical course in France or Switzerland.

Dr A. Bellerive (Haiti) succeeds Dr McKenzie Pollock as senior W.H.O. representative.

In Geneva, the 26th session of the Executive Board opened on Oct. 25. Dr Henrique M. Penido (Brazil) was elected chairman.

THE WORLD'S FOOD

"Food and population are two of the crucial determinants of the future of mankind. Freedom from hunger in the less developed countries of the world, however, is not simply a matter of regaining or maintaining pre-war levels of per caput production and consumption. ... Much greater increases in food production in these regions are needed before any real progress can be made in stamping out hunger and malnutrition. But increased food production must go hand in hand with general economic development so that consumers can afford the additional food and the better quality food they need."

In these words, taken from his foreword to F.A.O.'s latest annual report,[1] the Director-General summarises the agricultural problem confronting the greater part of the human race. While the highly developed countries continue to increase production (to the point of accumulating surpluses) by

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[1] Registrar General's Weekly Return no. 42, 1960. H.M. Stationery Office. Pp. 204. 1s. 6d.

[1] The State of Food and Agriculture 1960. F.A.O., Rome. Pp. 182. 10s. Obtainable from H.M. Stationery Office.

A Medical Staff Residence

On Oct 18, at Odstock Hospital, Salisbury, a new residence for medical staff was officially opened by Mr P G Templeman, chairman of the Wessex Regional Hospital Board

The residence has 17 bed sitting rooms each with its own wash-hand basin and built in furniture A large lounge is separated from the dining room by sliding doors and meals are served from a small service kitchen adjoining the dining room There is a library away from the living-room area Two flats for married residents have been built beside the new residence The flats are furnished and centrally heated, and each has a lounge/dining room, kitchen, main bedroom, and spare room The cost of the whole scheme, including furnishings, was £35,000

Award for Medical Film

La Presse Médicale is again offering a prize (1000 NF) for a medical 16 mm film whose time of projection does not exceed 30 minutes Films should be sent to the journal, 120, boulevard Saint-Germain, Paris VI^e^, before Feb 1

Caloric Balance in Man

The Nutrition Society is to hold a symposium on this subject on Saturday, Dec 17, at the Middlesex Hospital Medical School, London, W 1 The speakers will be Dr J V G A Durnin, Dr O G Edholm, Dr Raymond Greene, Dr I M Chalmers, Dr G C Kennedy, Dr A M Thomson, Dr F E Hytten, and Dr E M Widdowson Further particulars may be had from the hon programmes secretary of the society, Miss D F Hollingsworth, c/o Ministry of Agriculture, Fisheries and Food, Great Westminster House, Horseferry Road, S W 1

A meeting of the Biochemical Society is to be held on Friday, Nov 18, at 10 A M, at the Middlesex Hospital Medical School, London, W 1, when there will be a colloquium on histochemistry

Professor J B Duguid, who has lately retired from the chair of pathology in the University of Durham, has left for Malaya, where he is to be an adviser in histopathology under the Technical Cooperation Scheme of the Colombo Plan

The Association of Universities of the British Commonwealth (36, Gordon Square, London, W C 1) have published a list of fellowships, scholarships, and grants tenable at universities in the United Kingdom and a short list of awards tenable outside the United Kingdom Copies are being sent to universities and libraries and to other institutions on request

A committee meeting of the Group for Representation of the Views of Clinical Psychiatrists will be held on Thursday, Nov 10, at 5 30 P M, at Tavistock House North, Tavistock Square, London, W C 1

The London Medical Exhibition will be held in the New Hall of the Royal Horticultural Society, Westminster, from Nov 11 to 18

University College London will hold a reunion dinner at the college on Friday, Feb 17, for undergraduates or postgraduates who entered before 1918 Early applications for invitations should be made to the assistant secretary of the college, Gower Street, W C 1

From Nov 21 the address of the National Council for the Unmarried Mother and Her Child will be 255, Kentish Town Road, London, N W 5

Film about Handicapped Children—The Cine Club of Bristol, with the help of the South Western Regional Hospital Board and the Bristol education and health committees, has produced *Claremont*, which shows how children with spastic disabilities are educated and treated at a school at Claremont, Bristol The film, which is in 16 mm colour, has a sound commentary and lasts about 12 minutes The hiring fee is 1 guinea Applications should be sent to the medical officer of health, central health clinic, Tower Hill, Bristol, 2

CORRIGENDUM *Treatment of Urticaria*—The dose of proguanil ('Paludrine') mentioned in Sir Charles Dodds' letter of Oct 22 should have been 0 1 g (100 mg)

Diary of the Week

NOV 6 TO 12

Monday, 7th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W 12
1 P M Dr Brian Ackner Diagnosis of Depressive Illness

Tuesday, 8th

UNIVERSITY OF LONDON
5 P M (London Hospital Medical College, Turner Street, E 1) Dr Preston A Wade (Cornell University) Recent Advances in Fracture and Accident Services

ROYAL SOCIETY OF MEDICINE 1, Wimpole Street, W 1
5 30 P M *Experimental Medicine and Therapeutics* Dr A J Buller, Dr O C J Lippold Normal and Abnormal Willed Movement
8 P M *Psychiatry* Dr J J O Dwyer Dr Elliott Jaques Use of Psychiatric Skills in Industrial Organisations

BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr W M Court Brown Chromosome Analysis and Clinical Medicine

ST MARY'S HOSPITAL MEDICAL SCHOOL W 2
5 P M (Wright Fleming Institute) Mr D G Bonham Non malignant Enlargement of the Ovary

INSTITUTE OF DERMATOLOGY, Lisle Street W C 2
5 30 P M Dr O L S Scott Anomalies of Pigmentation

MANCHESTER MEDICAL SOCIETY
8 P M (Clinical Sciences Building York Place) *Surgery* Mr Ambrose Jolleys Treatment of Peripheral Tuberculous Glands Dr H B Andrews Tuberculous Glands

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M (General Infirmary at Leeds) Dr Paul Sandifer Involuntary Movements in Children

Wednesday, 9th

UNIVERSITY OF LONDON
5 30 P M (London School of Hygiene and Tropical Medicine) Dr Charles Wilcocks Aspects of Medical Investigation in Africa—Trypanosomiasis (Third Heath Clark lecture)

POSTGRADUATE MEDICAL SCHOOL
2 P M Dr P J Randle Regulation of Carbohydrate Metabolism by Hormones and Other Factors

INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Skin Cancer

INSTITUTE OF DISEASES OF THE CHEST, Brompton S W 3
5 P M Dr Paul Wood Present Position of Anticoagulant Therapy

MANCHESTER MEDICAL SOCIETY
5 P M (Medical School University of Manchester) *Pathology* Dr Leon Poller Pathogenesis of Thrombosis

UNIVERSITY OF LEEDS
5 P M (General Infirmary at Leeds) Miss U M Lister Placenta
6 P M Mr T T Redman Inefficient Uterine Action

ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH 9 Queen Street Edinburgh
5 P M Lord Cohen of Birkenhead Changing Concepts of Diathesis in Medicine (Frederick Price lecture)

Thursday, 10th

ROYAL COLLEGE OF SURGEONS, Lincoln's Inn Fields, W C 2
5 P M Dr Wade Accident Surgery of Motorways (Watson Jones lecture)

UNIVERSITY OF LONDON
5 30 P M (London School of Hygiene and Tropical Medicine) Dr Wilcocks Aspects of Medical Investigation in Africa—Implications (Last Heath Clark lecture)

ROYAL SOCIETY OF MEDICINE
5 P M *Ophthalmology* and *Dermatology* Dr G B Dowling, Dr J A Dudgeon Mr F S Perkins Behcet's Disease Dr I B Sneddon Mr Barrie Jones, Mr Frederick Ridley, Sir Benjamin Rycroft Bullous Conditions of the Skin and Conjunctiva

BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Dr M R Pollock Physiological Adaptation in Micro organisms

ALFRED ADLER MEDICAL SOCIETY
8 P M (11, Chandos Street, W 1) Mr Lewis Way *Problems of Social Psychology*

CECIL GORDON LECTURE
5 P M (University New Buildings, Teviot Place, Edinburgh) Prof Lancelot Hogben Nature Nurture Issue and the Medical Curriculum

HONYMAN GILLESPIE LECTURE
5 P M (University New Buildings, Teviot Place, Edinburgh) Mr J H S Scott Accident Services

UNIVERSITY OF ST ANDREWS
5 P M (Physiology Department Queen's College, Dundee) Prof M F A Woodruff Outlook for *Transplantation of the Kidney in Man*

Friday, 11th

POSTGRADUATE MEDICAL SCHOOL
10 A M Mr A J C Latchmore Surgery of the Biliary Tract
1 P M Prof W S Peart Ischaemic Kidneys in Hypertension

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330 Gray's Inn Road, W C 1
3 30 P M Dr D A Osborn Disorders of the Blood in E N T Practice

Appointments

BOYD J M, M B Glasg, D P H depute M O H, Renfrewshire

DARLOW A R, M B Lond, D P H, D C H, D T M & H divisional M O Bedfordshire

GRAHAM P A M B Glasg F R C S consultant ophthalmologist, United Cardiff Hospitals and Welsh Regional Board Hospitals

HAINES CICELY R M B Sheff, D OBST assistant M O H and school M O Bournemouth

SPENCER P M, M B Lond, F R C S M R C O G D OBST consultant obstetrician and gynæcologist Elizabeth Garrett Anderson Hospital London

THOMSON R B M D Durh, M R C P consultant physician Royal Victoria Infirmary Newcastle upon Tyne

TURNER WARWICK MARGARET E H D M Oxon M R C P consultant general physician Elizabeth Garrett Anderson Hospital London

WRIGHT, D G M B Glasg F R C S E consultant orthopædic surgeon Durham group of hospitals

The Lancet · Saturday 12 November 1960

PREPARATION FOR THE PROFESSION *

The Present and the Future

JOHN ELLIS
M B E , M A , M D Cantab , F R C P
PHYSICIAN TO THE LONDON HOSPITAL, LONDON, E 1, AND TO THE PRINCE OF WALES GENERAL HOSPITAL, SECRETARY TO THE ASSOCIATION FOR THE STUDY OF MEDICAL EDUCATION

THERE are periods in the history of every country when the form of medical education is appropriate to the pattern of medical practice, and when that pattern is itself suitable to the medicine of the day, so that all knowledge can be applied effectively and ethically The standard of medicine is then as high as the degree of knowledge will allow, for medicine is in balance

Such a period comes to an end when there is a major advance in medical knowledge This advance passes very rapidly into practice and changes the pattern of it The change of practice then alters medical education, and if all goes well balance is restored

It is our particular good fortune to belong to medicine when it is again changing, or to be accurate has just changed The increase of knowledge has enforced specialisation—which itself ensures that knowledge will continue to grow at speed But, because in Britain no-one now lives far from a specialist, the general practitioner is prevented from doing much of the therapeutic job he was trained for Instead, he is left with an overwhelming amount of other problems of diagnosis, treatment, and prevention of disease, for which he was not trained He must transfer many patients to the care of another doctor, and he must be sure that he chooses the right specialty

While this increase in knowledge has thus been altering the pattern of practice, a change in the quality of knowledge has altered the doctor's concept of disease His attitude to diagnosis and treatment has become more scientific

But it must be noted that the change is in attitude to disease and not in attitude to the patient The problem of medical education is how to inculcate the scientific attitude while maintaining the highest standard of clinical skill and the most humanitarian concern for the patient as a person

* * *

It took us quite a long time to accept that with the coming of specialisation had come the end of general practice as we knew it, and also the end of the apprenticeship training which it had evolved for itself During that time an inevitable disruption of medical education has been intensified, more in some schools than others, by our continuing to produce general practitioners of a kind no longer required, by a system of apprenticeship to specialists which could not be successful anyway

However, that era of uncertainty as to the aims and objects of medical education is over It ended, in fact, several years ago when the General Medical Council in its *Recommendations* of May, 1957, officially stated that the aim is no longer to produce, by the time of qualification, a finished doctor of any kind In future medical education, for family doctors as well as for specialists, is to consist of two portions, undergraduate and postgraduate The significance of this radical change has not yet been fully appreciated for several reasons One is that a year of internship after qualification had become compulsory before 1957, and therefore the G M C 's action appeared to some to be no more than giving official blessing to something which had already happened A second is that, because medical education in this country is very rarely the primary concern of anyone, very many of those actively engaged in it have not yet read the G M C 's recommendations A third is that, in contrast to all its previous announcements the G M C did not specify in detail the nature of either a minimum undergraduate education or a minimum postgraduate training It very wisely left the onus of creating a new pattern of undergraduate education to each individual university and medical school, stating that this pattern must provide a sound basis for further study, by ensuring that the student not only acquires knowledge and clinical skill but also scientific method, he is to be given an education as well as a training This freedom is obviously essential if each of our 26 schools is to be able to develop new enterprise to the best of its capabilities, but initially of course it can act as a stimulus to progress only in those schools where the desire for progress exists

Thus, though medical education in this country has passed out of the phase of catabolism into the phase of anabolism, the signs of this are not to be seen in every university Some schools have set a new course for a new educational objective and are under way, some are drifting out of control, some are in the doldrums, and some are being blown far off course—even off their original course—by the contrary winds of contemporary medical practice It is inevitable that some will have a greater proportion of teachers who are firmly attached to the old form of training, but it is equally inevitable that these teachers, by their resistance to change, will demolish the pattern they seek to preserve It is natural that those schools which have been most successful in the application of one method should be the last to realise that it does not work any more The man who has for years travelled to his destination in a Rolls-Royce does not think of getting rid of it—until he discovers that others are getting there more satisfactorily in an aeroplane—with Rolls-Royce engines, of course

There is therefore cause for neither surprise nor lament in our present state of medical education, save in one respect Speed of adaption is obviously important and it does appear that this could be unnecessarily slowed in London About half of our medical students receive at least their clinical training in the 12 London medical schools Inequitable as it may seem, a faculty which has 12 separate schools is unable to move 12 times as fast as other universities, and is more likely to resemble a convoy whose speed is always that of the slowest ship It is always difficult for the commodore of a convoy to give the order " All ships to proceed at their best speed " It is true that in this case precisely that order has been given to the whole medical-education navy by the G M C , but there is in this country a well-known precedent for turning a blind eye to the receipt of a naval signal

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* Extracts from the Wood-Jones lecture delivered in the University of Manchester Medical School on Feb 9, 1960 An abridged version of the lecture appears in the October issue of the *Manchester Medical Gazette*

However, all schools have been charged with the duty of adapting their education to meet modern conditions and needs, and most have already begun to do this.

At first sight they appear to be up against an insuperable difficulty—that of deciding how much knowledge and how much training is to be in the undergraduate years, and how much in the postgraduate. These questions seem difficult to answer in view of the fact that the responsibility for the postgraduate years is shared by the university with many other organisations, including the Royal Colleges and the Ministry of Health, and no one of them has sole authority. Furthermore, nobody could at the moment be precise as to how much knowledge and how much technical skill is necessary for the minimum effective practice of any branch of medicine, particularly as the function of the family doctor is not yet clearly defined.

But the fact that we do not know these things need not inhibit the reform of undergraduate education at all. For the aim of this, now, is first and foremost to *educate*—i.e., to give the student *not* knowledge but the power to utilise knowledge.

That he must know facts is obvious, and that in his early days he cannot find these out for himself but must be given them is equally obvious. His and his teachers' primary purpose, however, must be that he learns how to learn for himself. Therefore the factual content of the undergraduate period does not have to be any particular percentage of the total of medical knowledge; it has to be chosen for its relevance to future learning, not for its relevance to future practice. Equally important, the student's progress must be assessed *primarily* on his ability to reason and utilise knowledge, and not merely in terms of the amount he knows. Similarly his clinical proficiency must be judged on the soundness of his method, of which the correctness of the physical signs he elicits from a patient in an examination is but one indication. By the same token, if it be true, as is sometimes claimed, that the newly qualified of today know more than their predecessors ever did, this does not mean that all is really well with medical education.

If the object of undergraduate education is achieved, then gaps in knowledge and inadequacy of technique will be made good in the postgraduate period. If the object of undergraduate education is not achieved, then such gaps will probably remain for ever, and he will be largely denied the mastery of new data and the critical evaluation of new treatment. Though specialisation has come to stay, there is nothing the least static about the size or form of any particular specialty. The future happiness and success of specialist and general practitioner alike depend on his ability to learn and on his knowledge of general principles.

The following should be our objectives:

1. The student must learn how to learn for himself.
2. He must acquire a scientific method of thought—i.e., the power to reason and think critically.
3. He must achieve competence in clinical method—i.e., the techniques of obtaining information from patients.
4. He must gain an understanding of the responsibilities of a professional person.

If these objectives are reached the student will inevitably have built up a foundation of knowledge, including empirical knowledge. He will also have built a foundation of clinical experience, as regards the diagnosis, treatment, and prevention of disease on the one hand and the nature of man on the other. The exact content of the foundations of knowledge and experience will vary, but during the years of his postgraduate training, each student will be able to fill in those gaps relevant to his own future practice.

* * *

The undergraduate course of studies, thus freed from the need to include all or even any fixed percentage of knowledge and technique, can now, and must now, be based on considerations of the processes of learning.

This granted, it is at once evident that many different arrangements of studies have much to commend them in theory. Until they have been tried in practice, there can be no way of judging between them, and in any case the judgment can be no more than a clinical one. It is therefore idle to speak of the curriculum as though there is somewhere a correct arrangement which will be correct for every school and every student. The best curriculum for any particular school is that which enables it to make the best educational use of all its facilities and enables its students to progress through successive stages of learning, each with a clearly defined objective.

The number and sequence of stages, together with the purpose and content of each, will vary from school to school, but there are certain requirements which must be met in every stage everywhere:

1. Its purpose must be equally clear to both teachers and taught.
2. There must be deployed in it those incentives to study which are relevant to that purpose.
3. There must be built into it such forms of assessment of the student's progress as are appropriate to its content.

It goes without saying that other objectives, contrary incentives, and inappropriate tests should be excluded as rigidly as possible.

A course of studies of this kind cannot be made by a mere alteration of the timetable, even if this is done with educational objectives in mind. An entirely new attitude to teaching is required, and reform of the curriculum will be ineffectual unless there is also a reform of the method by which the curriculum is devised, applied, and constantly assessed. In my opinion this is no longer a matter of administration from the dean's office. There is required for each stage of the course a team of men who are responsible for it. They should represent all those departments most closely concerned with that stage, together with others whose advice could be helpful, even if they are not likely to teach in it themselves. For example, preclinical teachers should be concerned with the planning and assessment of predominantly clinical stages, and clinicians with the predominantly preclinical stages.

The team should, moreover, be representative of whole-time and part-time teachers, thus ensuring that the largest possible number of all kinds of teacher are closely involved in the educational effort. In this way cooperation can be achieved, for, instead of every department competing for what it feels is its rightful portion of the student's time, each becomes more concerned with what it has to contribute to the common purpose of each stage of the student's development. Furthermore, it is only when a teacher is able to appreciate the overall picture of that development that he can judge at what stage his own subject can make its best contribution. At present the resources of a special department are often squandered because students are routed through it too early or too late. Frequently also a student is able to attend a department for one period only, although it has something to offer him at several stages.

The effective planning, execution, and frequent assessment of every stage of a real course of studies is quite beyond the capabilities of anv dean's staff or curriculum committee, but every school could muster a team for each stage Each team would be working towards a comprehensible and realisable objective, and would be able to define the content of knowledge and practical experience, deploy relevant incentives, and devise appropriate forms of assessment If integration of staff were ensured, the student would be helped to integrate his knowledge for himself without the aid of elaborate timetable innovations —and neither the autonomy of departments nor the freedom of individual teachers would be lost

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I do not imagine that there will be anything very fanciful about the objectives of any stage, nor anything very intricate about its organisation It is possible already to see the general outline in several schools, and I would imagine that our traditional respect for sound clinical method based on an uninterrupted introduction to it will result in most universities preferring not to bring clinical experience very far forward in the course Indeed one would expect the first stage to continue to be one of the study of the normal, based on the old preclinical departments together with new ones, such as genetics The preclinical departments already form a kind of stage committee in most schools, but the addition to it of clinical and other representatives would, without necessarily taking part in the teaching at all, go far to create that unity of purpose, common outlook, and single terminology at staff level, without which students' work will remain divided into preclinical and clinical

Later stages must of course continue to be based upon existing firms and departments, but the great strength of these will be fully utilised if all concerned know what they are trying to do For example, a stage devoted to practice of clinical method must obviously use general inpatient firms, but the teachers on these firms would not be left, as now, to try to grapple with all aspects of medicine, and would have instead agreed limited objectives together with a chance to assess their results Nor would they have to contend and compete with synchronous courses of instruction, of which neither the content nor the purpose was known to them

It is in the later part of the present clinical curriculum that confusion and dissipation of effort are now so marked, particularly in regard to the purposes of outpatient experience and the contribution of special departments Order can be created again out of near-chaos by this simple process of organising stages of learning and experience by groups of teachers responsible for them

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Our peculiar system of hospital staff structure has provided us with a teaching device in the firm, which ensures that a small number of students are closely attached to a teacher who is personally responsible for them and for the patients with whom they are concerned The student is thus constantly reminded that the care of the individual patient is the yardstick by which everything else is measured He is able to learn of the professional responsibilities of a doctor by the only possible method—observing the doctor fulfilling them Above all, the welding together of his education and practical training is assisted by his being required to focus both his integrated knowledge and his practical skill upon the problems of his patients He is enabled to acquire empirical knowledge and experience and at the same time be encouraged to learn scientific method because his teacher can set him this example, can excite his curiosity, and can guide him as an individual through his personal difficulties of learning

It is small wonder that other countries are endeavouring to create for educational purposes this firm system which considerations of hospital practice developed here Unfortunately with us it has been weakened by many factors which we have not tried to offset The first of these is simply that the clinical teacher has not got the time which is required for the care of both his patients and his students The second is that we have continued to think of the firm as an inpatient organisation

I believe that part of the last clinical year should be devoted to a stage of learning by experience under supervision, and that this should be based on attachment, for at least four months to a general medical firm, primarily in the outpatient department but extending into the wards In this students should be responsible for individual patients as they now are on the traditional inpatient firm Student and patient together would visit the special departments as the patient's condition demanded, and both would return to the doctor responsible for both

At this stage it should also be easy to extend the student's experiences outside the walls of the hospital, to give him an understanding of the patient as a whole, and demonstrate the relation of medicine to the community It is here that I would incorporate the general practitioner into the undergraduate teaching team, with membership of the committee responsible for this stage, so that he is conversant with the objectives which the student has been set and with the lines on which his development is planned

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The provision of a new curriculum and a new type of administration, however, will not completely solve the problem of readapting medical education to present conditions of medicine The inclusion into undergraduate medical schools of all that is meant by university education is also necessary An essential requirement of this is interest in the individual student, so that he may develop in a stimulating intellectual atmosphere, with the encouragement and guidance of his teachers It would be idle to pretend that this is now possible in all our schools

If the medical student is to be a university student, then he must be treated as such, and the medical school must provide not merely teachers, a curriculum of classes, and an administration, but also an educational service It is not enough to have a tutorial system which is a mere adjunct to the other forms of teaching The system providing encouragement and guidance must not be separate from the system of reproof, which is represented by authority and vested in the dean Any dichotomy can only result in resentment of authority or frustration of encouragement But if all good incentives are mobilised and coordinated into one discipline, then progressive assessment of the individual becomes possible, and he can be given such help as he is known to need The medical school must have some kind of director of studies as well as a dean—just as our older university colleges have a senior tutor as well as a master—tutors and supervisors as well as teachers

The increased need for education requires also a new attitude to halls of residence In many universities these have long been recognised as a means whereby students can educate themselves by indirect contact with several faculties In his later years, however, the medical student

However, all schools have been charged with the duty of adapting their education to meet modern conditions and needs, and most have already begun to do this

At first sight they appear to be up against an insuperable difficulty—that of deciding how much knowledge and how much training is to be in the undergraduate years, and how much in the postgraduate These questions seem difficult to answer in view of the fact that the responsibility for the postgraduate years is shared by the university with many other organisations, including the Royal Colleges and the Ministry of Health, and no one of them has sole authority Furthermore, nobody could at the moment be precise as to how much knowledge and how much technical skill is necessary for the minimum effective practice of any branch of medicine, particularly as the function of the family doctor is not yet clearly defined

But the fact that we do not know these things need not inhibit the reform of undergraduate education at all For the aim of this now, is first and foremost to *educate*—i e , to give the student *not* knowledge but the power to utilise knowledge

That he must know facts is obvious, and that in his early days he cannot find these out for himself but must be given them is equally obvious His and his teachers' primary purpose, however, must be that he learns how to learn for himself Therefore the factual content of the undergraduate period does not have to be any particular percentage of the total of medical knowledge, it has to be chosen for its relevance to future learning, not for its relevance to future practice Equally important, the student's progress must be assessed primarily on his ability to reason and utilise knowledge, and not merely in terms of the amount he knows Similarly his clinical proficiency must be judged on the soundness of his method, of which the correctness of the physical signs he elicits from a patient in an examination is but one indication By the same token, if it be true, as is sometimes claimed, that the newly qualified of today know more than their predecessors ever did, this does not mean that all is really well with medical education

If the object of undergraduate education is achieved, then gaps in knowledge and inadequacy of technique will be made good in the postgraduate period If the object of undergraduate education is not achieved, then such gaps will probably remain for ever, and he will be largely denied the mastery of new data and the critical evaluation of new treatment Though specialisation has come to stay, there is nothing the least static about the size or form of any particular specialty The future happiness and success of specialist and general practitioner alike depend on his ability to learn and on his knowledge of general principles

The following should be our objectives

1 The student must learn how to learn for himself

2 He must acquire a scientific method of thought—i e , the power to reason and think critically

3 He must achieve competence in clinical method—i e , the techniques of obtaining information from patients

4 He must gain an understanding of the responsibilities of a professional person

If these objectives are reached the student will inevitably have built up a foundation of knowledge, including empirical knowledge He will also have built a foundation of clinical experience, as regards the diagnosis, treatment, and prevention of disease on the one hand and the nature of man on the other The exact content of the foundations of knowledge and experience will vary, but during the years of his postgraduate training, each student will be able to fill in those gaps relevant to his own future practice

* * *

The undergraduate course of studies, thus freed from the need to include all or even any fixed percentage of knowledge and technique, can now, and must now, be based on considerations of the processes of learning

This granted, it is at once evident that many different arrangements of studies have much to commend them in theory Until they have been tried in practice, there can be no way of judging between them, and in any case the judgment can be no more than a clinical one It is therefore idle to speak of the curriculum as though there is somewhere a correct arrangement which will be correct for every school and every student The best curriculum for any particular school is that which enables it to make the best educational use of all its facilities and enables its students to progress through successive stages of learning, each with a clearly defined objective

The number and sequence of stages, together with the purpose and content of each, will vary from school to school, but there are certain requirements which must be met in every stage everywhere

1 Its purpose must be equally clear to both teachers and taught

2 There must be deployed in it those incentives to study which are relevant to that purpose

3 There must be built into it such forms of assessment of the student's progress as are appropriate to its content

It goes without saying that other objectives, contrary incentives, and inappropriate tests should be excluded as rigidly as possible

A course of studies of this kind cannot be made by a mere alteration of the timetable, even if this is done with educational objectives in mind An entirely new attitude to teaching is required, and reform of the curriculum will be ineffectual unless there is also a reform of the method by which the curriculum is devised, applied, and constantly assessed In my opinion this is no longer a matter of administration from the dean's office There is required for each stage of the course a team of men who are responsible for it They should represent all those departments most closely concerned with that stage, together with others whose advice could be helpful, even if they are not likely to teach in it themselves For example, preclinical teachers should be concerned with the planning and assessment of predominantly clinical stages, and clinicians with the predominantly preclinical stages

The team should, moreover, be representative of whole-time and part-time teachers, thus ensuring that the largest possible number of all kinds of teacher are closely involved in the educational effort In this way cooperation can be achieved, for, instead of every department competing for what it feels is its rightful portion of the student's time, each becomes more concerned with what it has to contribute to the common purpose of each stage of the student's development Furthermore, it is only when a teacher is able to appreciate the overall picture of that development that he can judge at what stage his own subject can make its best contribution At present the resources of a special department are often squandered because students are routed through it too early or too late Frequently also a student is able to attend a department for one period only, although it has something to offer him at several stages

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The increased need for education requires also a new attitude to halls of residence. In many universities these have long been recognised as a means whereby students can educate themselves by indirect contact with several faculties. In his later years, however, the medical student lingers on after his colleagues in other disciplines and tends to become more attached to a hospital than a university. Those who have no home in the vicinity may live in a hostel belonging to the medical school, but such hostels, as their name implies, are often thought of as merely lodging-houses conveniently near the wards. There is a great need for a change of attitude so that these places can play their full part in education. All students should spend some time in them, and not merely those who have difficulty in finding accommodation elsewhere. Far greater responsibility for the corporate life of the student body should then be given to the students themselves—a necessary experience for those who are going to carry heavy professional burdens but who now tend to be kept from both responsibility and community life up to the age of 24. In this field also the teaching staff have a large part to play, not as persons of authority or with administrative duties, but as senior members of a single professional and intellectual community.

In none of these things, which I believe to be so important, do I envisage any kind of spoon-feeding or wet-nursing of students. On the contrary, I am advocating that they be regarded much less as groups of overgrown schoolboys, and much more as individual adult members of a profession. Their reactions to the education offered must be regularly sought, as in most other countries it now is, and they should feel free to seek advice on problems of learning without fear of jeopardising their careers. In the past medical schools have been so concerned with teaching and examinations, that few facilities, either material or in personnel, now exist for education. The need for them is urgent, and they are required for the postgraduate as well as the undergraduate. The days have passed when any medical school can feel that its responsibility for a man has ended when he has passed his final examinations.

" Finals ", of course, are now a misnomer, for they merely indicate a qualification which is necessary before the student is in his last year of general internship, legally able to undertake the responsible practice under supervision of which this stage of experience is composed. It remains to be seen whether this stage should be increased in duration or advanced in time. But it is already a responsibility of the medical schools, though not one which they have been able fully to discharge. They will need to develop a much more active system of caring for the individual before they can do so.

It will only be when such a system has developed that many other features of a university education in medicine can be properly undertaken. For example electives, and opportunities for students to study a subject in depth by undertaking some piece of original work, depend for their full effect on adequate knowledge and guidance of the individual. Furthermore we have to regain in this country greater freedom for each student to develop in his own way and at his own speed. We have had an overcrowded curriculum for so long, that we have almost come at accept the idea of having the same timetable for every student. Worse still, the system of grants, by which most students are financed, has encouraged the idea, in both medical schools and grant-giving authorities, that there is a fixed maximum duration of studies which is properly common to all students. This is most unfortunate, because no-one has ever laid down more than a minimum period, and students do not all progress at the same speed. It is an odd paradox that by so rightly removing financial barriers to medical education in this country, we have at the same time removed from the individual his necessary freedom to vary from the average. In the United States where most students are privately financed, it is easier for a man to step off the production-line than it is here, where courses are repeated only by students who have done badly. In Sweden, where students can get State loans but not grants, the finishing line is an entirely personal affair. Our system of a class of students all taking their examination on the same day is regarded as most unusual.

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In my view readaptation of medical education depends then, on (1) a course of studies, based on stages of learning together with relevant forms of assessment, (2) a more effective method of operating and maintaining the new curriculum, and (3) a university atmosphere. If these three things are provided, then undoubtedly new teaching techniques will emerge, or at all events we shall learn much more than we now know about the problems of education and the answers to them. In order to set our house in order, however, we do not need any more information than we now have. It is as useless as it is dangerous to wait for scientific proof that this or that is necessary, or that one scheme is better than another. This is a matter for clinical judgment. It is futile, and really only a form of escapism, to wait for some magic concrete plan which can be put into administrative effect and then forgotten.

The main obstacle to the full implementation of these three things is that very few teachers have enough time in which to give undivided attention to education. This can be remedied only by ensuring that part-time clinical teachers particularly, have enough sessions at the teaching hospital to enable them to practise clinical medicine, educate students, and engage in research. It is essential that this is done, if the country is to continue to have a high standard of medical service. It will inevitably cost money, but medical education is important. It alone can pass the advances of medicine on into effective practice. It is hopeless and wasteful to tackle it halfheartedly, and the most economical medical school, like the most economical hospital, is the one which sets out to be the best rather than the cheapest.

If in the National Health Service we can but make the terms and conditions of service of medical teachers relevant to the demands of education, we shall be able to mobilise a quite remarkable number of assets. Indeed, we should be in a far better position than any other country to solve the remaining problems of medical education.

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It seems justifiable to expect, therefore, that after a long period of difficulty, we can now enter a period in which medical education will be once more in equilibrium with medicine. Certainly we should be able most successfully to give an education in medicine while retaining and even improving our ability to teach sound clinical method. But this does not mean that we will then be automatically giving a good preparation for medicine as a profession.

The basis of British practice is that each patient, whether in his home or at hospital, has one doctor who takes personal responsibility for him, but there is no doubt that this basis has been weakened, and that too often there is uncertainty as to who is really responsible for the patient. The doctor also has a responsibility to the community, which cannot be discharged merely by attending to individuals, and students have to be made aware of very many important duties of the profession other than that of diagnosing and treating disease. Lastly we have, always, the problem of the way in which we discharge our duties—the standard which the profession sets for itself and the nature of its corporate discipline.

In times of great change the standards of a profession are at risk, and all ethics have to be translated into new terms. Moral exhortation without content or direction is a futile thing, and today the student must be brought to share the problems which face his teacher both as concern the patient and the profession. He must learn that science, which he must use, searches only after truth and has no humanitarian ends in view; but he must also learn that in a *professional* community, unlike others, how a decision is made is more important than what is decided.

These problems are difficult—but only because medicine and the profession face a greater challenge than ever before. I would say that there has never been a better time than this in which to be a doctor: the opportunities, like the challenge, are greater than ever before. They are greater, I believe, in this country than in any other: we are in a better position to solve all our problems. But we cannot do so unless we set our sights high. We must accept that in a time of change the most idealistic approach is the most realistic. The pursuit of quality is the only aim proper to our profession and the only one it can afford to have.

THE EFFECT OF TEST FEEDS ON THE PLASMA LIPIDS

K. J. KINGSBURY
M.B., Ph.D. Lond.
SENIOR LECTURER

D. M. MORGAN
RESEARCH ASSISTANT

P. C. SHERRINGTON
RESEARCH ASSISTANT

THE SURGICAL UNIT, ST. MARY'S HOSPITAL, LONDON, W.2

It has been shown repeatedly that the type of fat in the diet affects the lipid content of the plasma. But the kind of investigation so far reported has several disadvantages.

The lipid changes have been produced by feeding particular oils and fats for several days, weeks, or even months, with the remainder of the diet under careful control; and in these circumstances several weeks elapse before the plasma lipids reach a constant level on the basal diet and again with each fat under test. Because during all this time the basal diet has to be rigidly controlled (Ahrens et al. 1957), many investigators have resorted to giving this diet as homogenised liquid feeds (Kinsell et al. 1953). Apart from the practical difficulties—especially for studies on normal people and outpatients—arising from long-continued control, the test materials may not be available in sufficient quantity, or may be unsuitable for long-term administration (e.g., tung oil). Moreover the effects of trace materials, and the relative importance of particular substances, are often difficult to evaluate when whole diets are being fed.

Hence, for identifying and defining the dietary factors that influence human lipid metabolism, there is need of a quick and reproducible biological test. This should last no more than 12 hours, for then only the test substance need be fed, the experimental conditions can be easily controlled, and any lipid changes can be compared with the effects of fasting for an equal period. Also, if the test is to be used as a method of biological assay, it should evoke reproducible responses in normal people and be sensitive to small changes.

Such a method, in this laboratory, has been in use for 4 years. Single test feeds of oils are given under standard conditions so that the effect of each oil on the plasma lipids can be quickly and clearly demonstrated. In this paper we illustrate the method first by describing the effect of arachis oil on the plasma glyceride, phospholipid, and cholesterol, and then by reporting the effects of various other oils.

Materials and Methods

The subjects were healthy male medical students (aged 19–33) on the same kind of diet and activity. They were not allowed dietary fat during the 12 hours before the experiment nor excessive fat on the previous day, and their fasting plasma was clear. A light breakfast of fat-free drinks, dry toast, and marmalade was allowed 2–3 hours before the experiment.

The Test Feed

50 g. of the oil is given as a single feed, emulsified with 50 ml. of skimmed milk and 50–100 ml. of tap water, and flavoured if desired. (With feeds of less than 30 g. the changes in the plasma lipids are small and inconsistent, while feeds above 60–70 g. often cause nausea without proportionately increasing the plasma-lipid changes.) The emulsions must not be oily or thick and should be at room temperature; they should be drunk quickly, without breathing through the nose. The feeds are followed immediately by a strong-tasting drink, such as blackcurrant cordial, and by an apple.

A standard procedure without unpleasantness is essential, for, if the subjects are nauseated, the absorption of the feed is apparently delayed and the plasma-lipid changes are prolonged and inconsistent.

Collection of Blood Samples

Samples were taken before the feeds, and at 1½, 3½, 5½, 7–9, and 24 hours after them. The blood was obtained by venepuncture using siliconed syringes and run into 3.8% sodium-citrate solution buffered to pH 7.4 (18 ml. of blood to 2 ml. citrate solution); the plasma was separated immediately by centrifuging and then stored at 4°C. The analyses were begun next day.

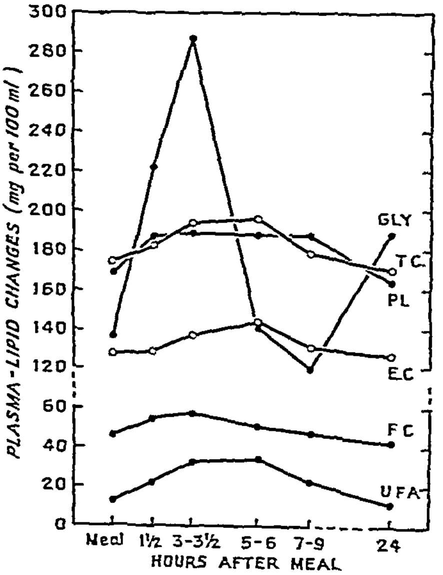

Fig. 1—The plasma-lipid levels before and after the 50 g. meals of arachis oil (mean of six results).

GLY, glycerides; T.C., total cholesterol; PL, phospholipids; E.C., esterified cholesterol; F.C., free cholesterol; U.F.A., unsaturated fatty acids.

Methods of Analysis

Lipid phosphorus was determined by the method of Fiske and Subbarow (Hawk et al. 1947), total and free cholesterol by that of MacIntyre and Ralston (1954), unesterified fatty acids according to Grossman et al. (1954), and plasma total esterified fatty acids by the method of Morgan and Kingsbury (1959).

The entire series of plasma samples from each individual, plus the various standards, were analysed together in triplicate. In this way fine differences between samples could be recognised. The coefficient of variation of replicate samples by each method has always been less than 0·8%. Total-cholesterol or *phospholipid changes of more than 3 mg. per 100 ml.* between the samples of one run, have therefore been accepted as significant.

Effects of Arachis Oil

After single feeds of 50 g. arachis oil the first observed change in the plasma lipids was an increase of glycerides, which reached a maximum 3–$3^{1}/_{2}$ hours after the feeds, after which the values fell rapidly for 3 hours and then more slowly and variably. This increase in glycerides was accompanied by a slower rise and fall of the plasma cholesterol, phospholipids, and unesterified fatty acids, which reached their maximum at 3–6 hours after the meals, decreased gradually in the next 3 hours, and then fell very slowly. The amount and the timing of the cholesterol and phospholipid changes were very similar. The behaviour of the plasma lipids is shown in fig. 1, which gives the average values obtained in six volunteers.

It has been found that if too little of the oil is absorbed, or if the oil is absorbed too slowly, the subsequent changes in the cholesterol and phospholipids are inconsistent and unpredictable. Adequate absorption of the oil, normally timed, is therefore a necessary condition of the experiment, and we do not consider it adequate unless the plasma glycerides rise between the fasting and $3^{1}/_{2}$-hour samples and fall between the $3^{1}/_{2}$-hour and $5^{1}/_{2}$-hour samples. Thus, if the plasma glycerides had not increased by more than 60 mg. per 100 ml. plasma (0·7 mMol. per litre) at $3^{1}/_{2}$ hours, and if over a third of this increase had not been removed by $5^{1}/_{2}$ hours, the experiment was rejected. The glyceride increases shown in our results represent, therefore, the differences between the fasting and $3^{1}/_{2}$ hour samples, and the percentage clearances are the percentage removal of these increases between $3^{1}/_{2}$ hours and $5^{1}/_{2}$ hours.

In normal subjects with a clear fasting plasma and a

CHANGES IN PLASMA-LIPID LEVELS CAUSED BY SINGLE FEEDS OF VARIOUS OILS

Type and number of feeds	Plasma-lipid changes (mg. per 100 ml.) average and range									Fig 2 no.	Iodine value of oil
	Glycerides		PL	TC	FC	EC	TC/PL	FC/EC	UFA		
	Increase	Decrease									
Group 1 Coconut (6)	144 *(106–257)*	46% *(38–62)*	23 *(20–25)*	27 *(24–29)*	11 *(9–12)*	16 *(15–17)*	1·12 *(0·96–1·4)*	0·69 *0·53–0·80*	17 *(14–24)*	1	8
Palm (4)	134 *(64–182)*	52% *(48–65)*	20 *(18–24)*	21 *(18–24)*	8 *(5–10)*	13 *(10–15)*	1·05 *(0·80–1·2)*	0·61 *(0·40–0·66)*	16 *(15–19)*	2 2	52
Arachis (18)	143 *(81–210)*	57% *(51–65)*	20 *(16–26)*	20 *(16–24)*	7 *(5–8)*	13 *(12–15)*	1·00 *(0·84–1·20)*	0·54 *(0·33–0·58)*	20 *(14–28)*	3	89
Olive (6)	179 *(123–234)*	50% *(42–56)*	21 *(19–24)*	19 *(18–22)*	6 *(5–9)*	13 *(12–15)*	0·91 *(0·85–1·1)*	0·46 *(0·38–0·59)*	19 *(15–26)*	4	83
Tung (2)	90 *(64–116)*	42% *(38–49)*	17 *(14–21)*	18 *(15–22)*	5 *(4–6)*	13 *(11–6)*	1·1 *(1·1)*	0·38 *(0·38–0·37)*	14 *(13–14)*	5	165
Group 2 Sunflower (5)	172 *(110–197)*	63% *(49–72)*	12 *(10–14)*	7 *(6–8)*	2 *(2–3)*	5 *(4–7)*	0·58 *(0·56–0·68)*	0·4 *(0·36–0·68)*	24 *(19–31)*	6	131
Safflower (3)	146 *(92–216)*	48% *(41–53)*	13 *(9–16)*	6 *(5–8)*	2 *(2–3)*	4 *(3–6)*	0·52 *(0·5–0·55)*	0·50 *(0·33–0·66)*	19 (12–28)	7	138
Corn (4)	138 *(103–157)*	51% *(41–62)*	14 *(11–15)*	6 *(4–8)*	2 *(2–3)*	4 *(3–5)*	0·43 *(0·4–0·65)*	0·50 *(0·4–0·7)*	21 *(19–26)*	8	113
Soya (2)	118 *(122–114)*	44% *(36–52)*	14 *(14–15)*	8 *(7–9)*	3 *(3)*	5 *(4–6)*	0·57 *(0·5–0·6*	0·60 *(0·5–0·75)*	21 *(17–25)*	9	134
Cotton-seed (2)	141 *(112–170)*	48% *(40–51)*	14 *(14–15)*	9 *(9–10)*	3 *(3)*	6 *(6–7)*	0·66 *(0·6–0·7)*	0·50 *(0·4–0·6)*	16 *(17–15)*	10	106
Whale (6)	166 *(100–158)*	68% *(53–79)*	14 *(12–16)*	6 *(4–8)*	2 *(1–3)*	4 *(3–5)*	0·48 *(0·4–0·58)*	0·5 *(0·36–0·64)*	21 *(11–28)*	11	128
Pilchard (3)	125 *(106–139)*	53% *(38–67)*	15 *(12–17)*	8 *(7–10)*	3 *(3–4)*	5 *(3–7)*	0·54 *(0·47–0·57)*	0·6 *(0·5–0·6)*	15 *(13–23)*	12	152
Heated tobacco seed (12)	160 *(64–256)*	56% *(45–59)*	10 *(5–15)*	5 *(2–10)*	1 *(0–3)*	4 *(2–8)*	0·50 *(0·21–0·57)*	0·25 *(0·0–0·6)*	20 *(12–26)*	13	136
Group 3 Stored crude tobacco-seed (12)	145 *(99–204)*	61% *(43–67)*	10 *(5–13)*	2·0 *(0–6)*	−3·0 *(−1–−6)*	5·0 *(2–10)*	0·20 *(0–0·7)*	−0·6 *(−1·2–−0·2)*	19 *(13–24)*	14	136
Crude tobacco seed (12)	188 *(72–470)*	62% *(49–78)*	0·25 *−5–+5*	1 *(−3–+3)*	−8·0 *(−3–20)*	9 *(+3–+20)*	4·0 *(−0·75–−2·0)*	−0·9 *(−0·8–−1·1)*	19 *(12–39)*	15	136
Fasting (12)	−24 *(+1–−68)*		−5 *(−2–−10)*	−6 *(−1–18)*	−3 *(−2–−4)*	−3 *(−1–−9)*	1·2 *(−0·66–+3·0)*	1·0 *(+0·2–+3·0)*	−3 *(+3–10)*	Not included in Fig 3	
Fraction A (2)	123 *(116–130)*	48% *(39–57)*	9 *(7–11)*	2 *(0–4)*	−2 *(−1–−3)*	4 *(1–7)*	0·2 *(0–−0·3)*	−0·5 *(−1·0–0·4)*	16 *(15–18)*		
Fraction B (2)	161 *(135–177)*	56% *(47–65)*	12·0 *(9–15)*	7 *(6–7)*	2·0 *(1–3)*	5 *(5–4)*	0·58 *(0·66–0·47)*	0·4 *(0·2–0·75)*	25 *(16–34)*		
Cod liver (2)	101 *(19–113)*	62 *(48–76)*	13 *(11–15)*	8 *(5–11)*	3 *(2–4)*	5 *(3–7)*	0·61 *(0·45–0·73)*	0·6 *(0·7–0·57)*	30 *(21–39)*		150

PL. = Phospholipids T.C. = Total cholesterol F.C. = Free cholesterol E.C. = Esterified cholesterol U.F.A. = Unsaturated fatty acids

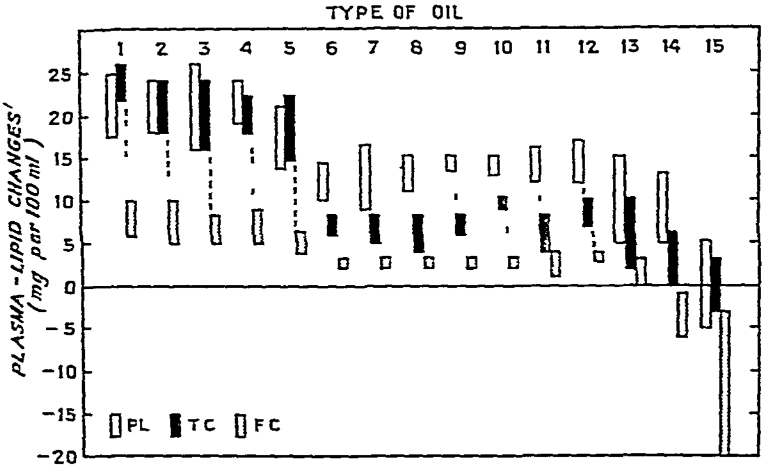

Fig 2

Fig 2—The changes in plasma phospholipid and cholesterol caused by the various oils (numbered as in table)

The effects of fractions A and B, cod-liver oil and of fasting, shown in the table are, for the sake of simplicity, not included in the figure.

PL.=phospholipids, T.C.=total cholesterol, F.C.=free cholesterol

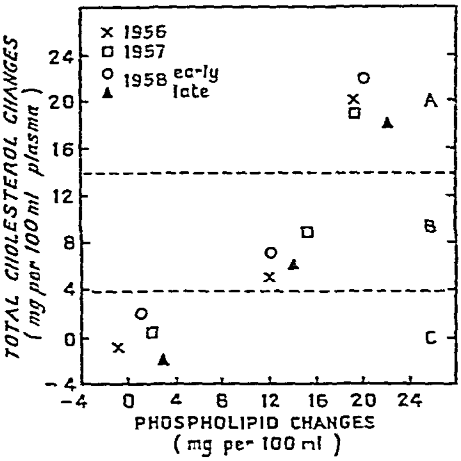

Fig 3

Fig 3—The response of three subjects to the same test feed when fed at intervals over 3 years

A, arachis, B, heated tobacco-seed oil, C, crude tobacco-seed oil

The fasting plasma levels of the three subjects were A, phospholipids 98 mg per 100 ml, total cholesterol 235 mg, B, phospholipids 158 mg, total cholesterol 169 mg, C, phospholipids 222 mg, total cholesterol 254 mg

normal absorption of glyceride, plasma cholesterol and phospholipid reached their maximum 3–6 hours after the feed. The changes in phospholipids and cholesterol caused by the feeds can be expressed by the values

$$\frac{(3^{1/2}\text{ hour}-\text{fasting})-(5^{1/2}\text{ hour}-\text{fasting})}{2}$$

The figure obtained in this way we call the lipid response.

Effects of Various Other Oils

Single 50 g feeds of other oils were fed in the same way to normal volunteers The oils used, the number of experiments, and the lipid response are shown in the table.

Non-polymerised refined tung oil was supplied by Unilever Co The other oils were of edible grade and obtained from Unilever Co, H M Faure & Co, British Cod Liver Oils Ltd, and through Hess Products and Cyclo Chemicals Ltd

Stored tobacco-seed oil is crude oil which has been stored at 4 C in the dark for 9 months and 'heated tobacco-seed oil' is the crude oil heated by steam to 165 C under a high vacuum

Fraction A' and "fraction B were prepared from the fatty acids obtained by dehydrating ricinoleic acid Those liquid below 10 C (Hilditch 1956) were stored at 0 C for several weeks in the dark in an atmosphere of nitrogen, a solid fraction was separated by filtration at 0 C Both liquid and soil fractions were then frozen at 20 C, stored at 0 C for several weeks, and filtered as before The fractions solid at 0 C were combined and called fraction A, the combined fractions were called fraction C They were fed as ethyl esters

With all the oils, plasma glyceride rose by more than 60 mg per 100 ml and over a third of this increase was removed at $3^1/_2$–$5^1/_2$ hours But the different oils produced three different types of lipid response, and can accordingly be placed in three groups (table and fig 2)

Group 1—These raised the total-cholesterol and phospholipid levels by about 20 mg per 100 ml., without altering the ratios of total cholesterol to phospholipid or of free cholesterol to esterified cholesterol.

Group 2—The increases in total cholesterol and phospholipid were smaller, but the ratio of total cholesterol to phospholipid was reduced. The ratio of free cholesterol to esterified cholesterol was unaltered.

Group 3—With the oils in this group (crude and stored tobacco-seed oil) the levels of phospholipid and total cholesterol rose only very slightly or actually *fell* The level of free cholesterol consistently fell, but both the phospholipid and the free-cholesterol/esterified-cholesterol ratios were variable.

These different lipid responses were not associated with differences in the amounts of glyceride increase

In control experiments a fat-free diet, taken for 24 hours, reduced the levels of all the plasma lipids estimated.

Reproducibility of Lipid Response

Fig 3 shows the changes in cholesterol and phospholipid levels obtained with oils of the three groups Each volunteer received one oil four times, and on each occasion it produced the same kind of response, distinct from the effects of the other oils In the experiment recorded in fig 4, each of four volunteers took three different oils All four subjects showed the same type of lipid response to a given oil, and similar alterations in response when the oils were changed. (In fig 4, for simplicity, only the cholesterol changes are shown.)

Thus healthy people gave the same lipid response to a particular type of oil, even when the tests were separated

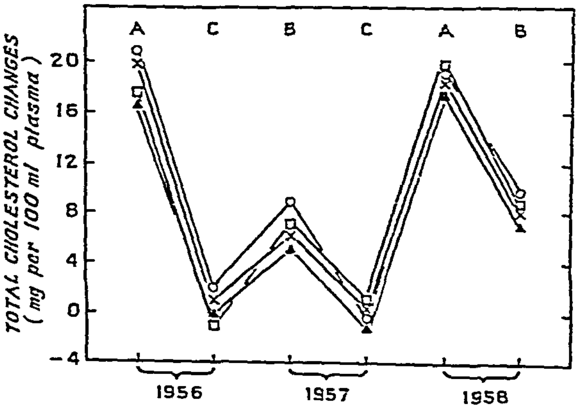

Fig 4—The "swing" of response in four subjects to three different types of oil (A, arachis B heated tobacco-seed oil C, crude tobacco-seed oil)

The fasting levels of total cholesterol in the four subjects were X, 181 mg per 100 ml, □, 211 mg ○ 183 mg, ▲, 189 mg by a year, and, by changing the oil, the volunteers could be "swung" to another response Clearly, the reproducibility of the results was not due to insensitiveness of the test This could in fact distinguish between the effects not only of different oils but even of the same oil before and after treatment by heat (table and fig 2)

Discussion

As a method of biological assay, the test feed has the advantage of simplicity, speed, and ease of control, and it enables us to ascertain the effects of single substances, using comparatively little material Their effects on plasma lipids are demonstrated not only (as in the longer experiments) by the changes in cholesterol and phospholipid but also by the relation of these lipids to one another and the relation of free cholesterol to esterified cholesterol The alterations in these relations are new findings which suggest that plasma-phospholipid and plasma-cholesterol levels are under separate physiological control Even in normal people the phospholipid/cholesterol ratio is not necessarily constant, and its different behaviour in response to group-1 and group-2 oils raises the interesting question whether it is ordinarily set by the diet

The different effects of crude and heated tobacco-seed oils is a further new finding, which will be discussed elsewhere The difference does not seem to be due to alterations in the fatty-acid composition of the oils

It is difficult to compare our results with those of other workers who have used single feeds for studying changes in the plasma lipids (Man and Gildea 1932, Lindholm 1956, Dole et al 1959), for, although Man and Gildea, for example, recorded similar phospholipid changes, their aim was to see whether lipid changes did in fact occur, and not to create a standard method of biological assay (Kingsbury 1958) Reasons why our findings may differ from those of the longer (more usual) experiments are numerous

1 The oils may have been subjected to different treatment (compare our different results with crude and heated tobacco-seed oils)

2 Most of the other work has been done on patients, whereas ours was on normal subjects

3 The results reported here concern only the period of lipid increase immediately following the fatty meals, whereas the results of long-term experiments must be the algebraic sum of varying lipid absorption, plasma-lipid increases, and clearance of lipids from the blood

4 The two methods may be sensitive to different variables

5 Whereas our results describe changes from a standard basal condition, the changes in the long-term experiments result from altering one diet for another This point can be illustrated by the fact that in the long experiments corn oil has so often caused an immediate and progressive fall in the plasma-cholesterol level, whereas in our experiments it caused a rise

It is all the more interesting, therefore, that our results should in many ways resemble those of Ahrens (1957), using the longer method In both investigations oils having iodine values above 100 produced low levels of plasma cholesterol, whereas with oils which have iodine values below 90 the cholesterol level increased with the saturation of the fat (see table) Whale, pilchard, and cod-liver-oil—which are rich in polyunsaturated acids but not in those essential for the normal health of animals (Thomasson 1953)—gave the same kinds of lipid responses as the edible vegetable oils (corn, soya, sunflower) whose high content of unsaturated acids is composed mainly of "essential" fatty acids This is similar to the results of Ahrens (1959)

In view of the similar effect of fish oils and vegetable oils on the plasma-cholesterol, it is interesting to reflect that, though an increase of tri-unsaturated acids in the tissue lipids of animals is strong evidence for a deficiency of the essential fatty acids (Jorgensen and Holman 1958), this accumulation of trienes has been reversed by cod-liver oil (Rieckenhoff et al 1949, Dam et al 1959), and that though this oil is rich in polyunsaturated acids, it has a very low essential-fatty-acid activity when assessed conventionally in terms of a normal skin in animals Thus it seems that many of the polyunsaturated acids, such as those found in cod-liver oil, may not only lower the blood-cholesterol level but also correct fatty-acid deficiencies

As conventionally defined, a "non-essential" acid very similar in physical properties to the "essential" linoleic acid is its *cis-trans* isomer, which has a melting-point of about −3°C (Privett et al 1955) or up to 7°C (Jackson et al 1952) Unfortunately it cannot yet be made in quantities sufficient for feeding experiments, but, as an alternative, we hoped to obtain low-melting-point isomers of linoleic acid from dehydrated ricinoleic acids (Hilditch 1956) Ultraviolet spectroscopic analysis (Hilditch et al 1951) of our fractions A and B showed that about 60% were linoleic acid or its isomers, of which about half were conjugated, probably the *cis-trans* isomers were concentrated in fraction B (melting-point 0–10°C) As both these fractions raised the plasma lipids only slightly (see table) it appeared that the lipid response to the natural *cis-cis* linoleic acid (approximately 70% of tobacco-seed oil) was neither prevented nor obscured by its conjugated or other isomers

Our results with tung oil are not at present explainable Sinclair (1959) has suggested that it should have the same effects as other non-essential oils of equal unsaturation, but this ignores its undoubtedly different properties, as evident in its chemical reactivity, rate of oxidation, and absorption spectra in the ultraviolet Possibly the biological action of conjugated fatty acids of this type differs from that of non-conjugated acids of equal unsaturation

The reasons for the different effects of the various oils are not yet established, but we cannot see why many factors in oils should not act in different ways For instance, the amount of the biologically essential linoleic acid usually given as a dietary supplement is about 50 g a day (Olson et al 1958) This would be about 5–10% of the total dry weight of the daily diet of our volunteers and probably about 10% of a patient's hospital diet In animals, however, severe essential-fatty-acid deficiency can be corrected by less than 0 5% of linoleic or arachidonic acid in the diet (Holman 1950)—an amount of arachidonic acid which is said to have no effect on the plasma lipids of man (Keys et al 1959) It may be that, in large amounts, unsaturated acids (both essential and non-essential) alter the physicochemical properties and hence the metabolism of their esters (glycerides, cholesterols, phospholipids, &c) (Klein and Martin 1959) This need not exclude a simultaneous correction of any existing fatty-acid deficiency (Fulco and Mead 1959)

In addition, an effect from the non-saponifiable or trace components of an oil cannot be excluded, and this may be the reason why crude tobacco-seed oil and heated tobacco-seed oil (though we have found no difference in their fatty-acid composition) have different effects

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In addition, an effect from the non-saponifiable or trace components of an oil cannot be excluded, and this may be the reason why crude tobacco-seed oil and heated tobacco-seed oil (though we have found no difference in their fatty-acid composition) have different effects

Summary and Conclusions

A method for the biological assay of dietary lipids is described in which changes in the plasma glycerides, cholesterol, and phospholipids are measured after single 50 g. feeds of the fat under investigation. Plasma samples are collected before and 1½, 3½, 5½, 7–9, and 24 hours after the test feed.

The conditions for success are a period of fat deprivation and a clear fasting plasma before the experiment, a standard method of feeding, the avoidance of nausea, and adequate absorption of the oil. The criterion of adequate absorption is a rise in plasma glycerides by more than 60 mg. at 3½ hours, of which increase over a third must have been removed by 5½ hours.

The plasma-cholesterol and plasma-phospholipid changes produced by the feeds are called the lipid response. This response differs with different oils, the characteristic changes being reproducible both in different subjects and in the same subjects after long intervals.

The method has the advantage of needing only small amounts of material, of being quick and sensitive, of easily allowing experimental controls, and of not requiring special diets.

It is not offered as an alternative to long-term experiment, but as a supplementary method especially useful for rapid biological assays.

New contributions by this method are (1) the finding that different oils have different effects on the plasma phospholipid cholesterol ratios, (2) the use of these changing ratios to classify the type of lipid response to the experimental fat, and (3) the different effects of crude and heated oils.

The reasons for the different effects of the various oils are not known, but they are unlikely to be all due to one type of substance or property.

We wish to thank the volunteers, without whom the work would have been impossible and who received no recompense for much unpleasantness, Mr W. Darrel and Mr P. A. Dupont for technical assistance, Prof. C. G. Rob and Mr R. W. Best (Unilever Ltd.) for advice and interest, and Bush & Co. for generous gifts of flavourings. Part of this work was included by K. J. K. in a thesis for the degree of doctor of philosophy, London University, 1958.

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MYOCARDIAL INFARCTION AMONG MEMBERS OF COMMUNAL SETTLEMENTS IN ISRAEL

DANIEL BRUNNER
M.D. Vienna

GIDEON MANELIS
M.D. Geneva

From the First Medical Department and Research Laboratory for Degenerative Cardiovascular Diseases, Government Hospital, Jaffa, Israel

THE incidence of ischæmic heart-disease differs strikingly between different countries (World Health Organisation 1956) and even in a single country between different ethnic and social groups (Brock and Bronte Stewart 1955, Brunner and Löbl 1957, 1958, Dreyfuss 1953, Toor et al. 1957).

We have sought to examine the influence of physical exercise on the incidence of myocardial infarction in the Kibbutzim and Kvutzoth. These are communal settlements in Israel, whose members are ethnically homogeneous and where the environmental conditions (standard of living, diet, housing, cultural activity, and recreation) are virtually uniform. No difference is made between teachers, clerks, businessmen, local political leaders, drivers, fishermen, masons, and agricultural workers.

Material and Methods

This survey covers the incidence of myocardial infarction in the ten years up to Dec. 31, 1959, in 8500 people (4500 men and 4000 women) who at the end of 1949 were aged 30–55.

One of us (G. M.) visited each of the 58 settlements in which these people lived. Because of the comprehensive medical service in these settlements, we had no difficulty in obtaining data on all fatal cases (sickness certificates, hospital case-records, postmortem reports, and electrocardiograms) and surviving patients who had had myocardial infarcts (detailed clinical examination and electrocardiograms). All patients except 2 were admitted to hospital soon after the infarction. Thus the diagnosis of myocardial infarction, whether the patient survived or died, was based on the clinical picture and on an unequivocal electrocardiographical diagnosis. As electrocardiographic proof of myocardial infarction we accepted only typical Q waves or typical T waves, or both together. Not included in this review are patients who presented the clinical picture of angina pectoris with or without the electrocardiographic pattern of coronary insufficiency.

Findings

In the ten-year period there occurred, among the population of 8500, 111 cases of myocardial infarction; 34 patients died and 77 survived. Of the 4000 women, only 9 had infarction, and of these 2 died and 7 survived.

In the communal settlements of all persons in the age-group of the sample, 30% are engaged in sedentary work and 70% in non-sedentary work. By contrast, in the cases of myocardial infarction, of the 34 who died 19 were engaged in sedentary work, and, of the 77 who survived, 42 were engaged in sedentary work. The group of non-sedentary workers included also those doing very light bodily work, such as that of confectioner or light physical work in industrial factories. When classifying the men according to their occupation, we took into account work done by the patient for at least four years before the attack. Particular care was taken not to include in this or any other group men who had changed their occupation as a result of their illness.

For non-sedentary male workers the annual incidence was 1.36 per 1000, whereas for sedentary male workers the annual incidence was 4.1 per 1000. Thus the incidence was three times greater in the sedentary workers. The

mortality-rate was likewise three times greater in this group

Comment

These data support those of Morris (Morris et al 1953, Morris and Crawford 1958) indicating the preventive influence of bodily activity

Jewish people are reputedly especially prone to ischæmic heart-disease (Epstein et al 1957), but our findings do not support this belief The annual incidence of myocardial infarction among the sedentary Jewish workers whom we studied is almost identical with that in London sedentary workers observed by Morris et al (1953) On the other hand, the incidence of myocardial infarction among non-sedentary workers in Kibbutz (0 8 per 1000 men per year) is only half the incidence among London postmen who walked in their daily work (1 6 per 1000 men per year)

These findings underline the importance of physical exercise as a factor in the prevention of myocardial infarction

This research was carried out with the aid of a grant from the Fund for Applied Research of the Israeli Ministry of Health and from the Research Foundation of the General Federation of Jewish Labour in Israel (Histadruth)

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World Health Organisation (1956) *Epidem vit Statist Rep* 9, 582

INVOLUTIONARY SCLEROSIS AND DIASTOLIC HYPERTENSION

EFFECT OF ENVIRONMENTAL CHANGE

A M Cohen
M D Amer Univ Beirut
LECTURER IN MEDICINE

E Neumann
M D Lausanne
INSTRUCTOR IN OPHTHALMOLOGY

I C Michaelson
Ph D Glasg , F R F P S , D O M S
PROFESSOR OF OPHTHALMOLOGY

From the Department of Internal Medicine B, and Department of Ophthalmology, Rothschild Hadassah University Hospital, Jerusalem, Israel

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The purpose of our investigation was to determine whether the difference in environment between Yemen and Israel also affects the prevalence of involutionary sclerosis and diastolic hypertension among these contrasting groups Yemenite Jews form particularly suitable material for this study, being a homogeneous group with little or no intermarriage with other groups Constitutional factors, therefore, cannot affect the clinical differences between the settled and the new immigrant groups

In order to have the groups unselected, the entire Yemenite population above the age of 30 in chosen areas were visited in their homes The diagnosis of diastolic hypertension was based on manometric examination, and that of involutionary sclerosis on ophthalmoscopic examination of the retinal vessels This procedure seems to be as reliable as any one method for the diagnosis of involutionary sclerosis, and is probably the most suitable for a house-to-house examination It is, however, appreciated that changes in the retinal blood-vessels do not necessarily indicate changes in the entire vascular tree, nor does the absence of any change rule out the possibility of arteriosclerosis in other parts of the body

Material and Methods

The survey was carried out during 1959 The first group, the " new immigrants ", consisted of the entire population, over the age of 30, in two settlements near Jerusalem, Yishi and Noham They had all immigrated from the Yemen within the past ten years The group contained 147 persons, 70 men and 77 women The second, the " settled " group, consisted of the entire population, over the age of 30, in two Jerusalem quarters, Nahalat Ahim and Mishkenot They all had lived in Israel for over twenty-five years, and some were born there This group contained 125 persons, 55 men and 70 women All examinations were carried out at their homes Age, sex, and time of arrival to this country were noted A short physical examination was carried out in each case Resting blood-pressure was taken several times Urine was examined for albumin with sulphosalicylic acid, and for glucose with glucose reductase (' Test Tape ', Lilly)

Diastolic hypertension was considered to be present when the systolic pressure exceeded 140–150 mm Hg, and the diastolic 90 mm Hg The criteria for involutionary sclerosis were (*a*) narrow retinal arteries, (*b*) unusually straight course of these vessels, and (*c*) narrowness of their bifurcations Many of these cases showed slight variations in calibre of the arteries, and some changes at the ateriovenous crossings These were not, however, thought to be essential for the diagnosis of involutionary sclerosis The arteries were considered to

TABLE I—AGE (YEARS) AND SEX-DISTRIBUTION IN THE TWO GROUPS

—	30–55 years				Over 55 years				Total	
	M		F		M		F		M	F
	Number of patients	Average age	Number of patients	Average age	Number of patients	Average age	Number of patients	Average age		
New	44	40 0 ± 7 8*	59	41 5 ± 7 3	26	69 2 ± 7 0	18	67 1 ± 8 0	70	77
Settled	30	40 7 ± 7 5	36	41 9 ± 8 3	25	68 1 ± 6 9	34	66 2 ± 7 1	55	70

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be narrow and straight if at least 2 out of the main 4 vessels in each fundus were found to be affected, and the bifurcations were considered narrow if the majority of them were affected There is a certain subjective element in the diagnosis of involutionary sclerosis in the retina, and therefore only cases where there was no doubt of the retinal diagnosis were included 60% of all cases of involutionary sclerosis showed systolic hypertension Fisher's exact method for a 2×2 contingency table was used for statistical analysis

Results

Table I shows the average age in each age-group for men and women is almost the same in the " settled " and " new immigrants " groups

4 cases of diastolic hypertension (3 women and 1 man) were found among the new immigrants, and 17 (7 men, 10 women) among the settled group There was no statistical difference between men and women in each age-group of the " new " and " settled " groups in the prevalence of diastolic hypertension or involutionary sclerosis, except for ages 30–55 Except in this group, men and women were grouped together (Fisher's exact method yields relatively low probabilities even for each sex and age group separately) The prevalence of hypertension is shown in table II

TABLE II—PREVALENCE (AS A PERCENTAGE) OF DIASTOLIC HYPERTENSION IN THE TWO GROUPS

—	30–55 years	Over 55 years
New	1% (0 M, 2 F)	7% (4 M 11 F)
Settled	7 5% (7 M 8 F)	20% (20 M, 21 F)
P	0 03	0 04

Proteinuria was found once in the 4 hypertensives among the new immigrants, and five times in the 17 hypertensives among settled Yemenites

It is of interest that, though there were no diabetics among the new immigrants, there were 9 among the settled group (6 men and 3 women), 8 being more than 60 years old

The percentage of cases with involutionary sclerosis, but without diastolic hypertension or diabetes, among the new immigrants and old settlers is given in table III

TABLE III—PREVALENCE (AS A PERCENTAGE) OF RETINAL INVOLUTIONARY SCLEROSIS IN THE TWO GROUPS

—	30–55 years			Over 55 years		
	Total	M	F	Total	M	F
New	3%	0	5	8%	9	6
Settled	18 %	7	27	34%	26	33
P		0 16	0 002		0 006	

There was a statistically significant difference in the prevalence of involutionary sclerosis between the " new " and " settled " in the age-group 55+ and between " settled " and " new " women in the age-group 30–55 No significant difference was found in the men of the age-group 30–55

Discussion

It can be seen that there is a greater prevalence of diastolic hypertension, and of the ageing process as seen in the retina, among the Yemenites who have lived in Israel for over 25 years as compared with Yemenite new immigrants who have not lived for more than 10 years in the country The findings parallel the differences in the prevalence of diabetes, and in the blood-cholesterol and blood-phospholipids estimates between both groups and confirm the impression that cardiovascular disease and arteriosclerosis are more prevalent in the settled group

There is a great difference between the conditions of life in Israel and in Yemen, and there is little doubt that the different prevalences of hypertension and involutionary sclerosis between the two groups is the result of these differences The lack of intermarriage with other groups of Jews eliminates constitutional and genetic factors as an explanation of the differences The main differences between the two groups are in food habits and in the general strain of living to which they are exposed The latter can be best described as the ambition for a higher standard of living, and the general " speeding-up " involved in the Western style of culture

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RADIOLOGICAL LUNG-FUNCTION STUDIES

R E STEINER
M D N U I, M R C P, F F R
DIRECTOR, DEPARTMENT OF RADIODIAGNOSIS

J W LAWS
M B Sheff, M R C P, F F R
HONORARY LECTURER IN RADIODIAGNOSIS

J GILBERT
A Brit I R E
CHIEF ELECTRONICS ENGINEER

M J McDONNELL
SENIOR
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DEPARTMENT OF BIOPHYSICS

HAMMERSMITH HOSPITAL AND POSTGRADUATE MEDICAL SCHOOL OF LONDON, LONDON, W 12

WE describe here a method of measuring and recording the changes in radiographic lung density during respiration We suggest that the function of a localised area of lung may be studied by correlating these density variations with simultaneous spirometric recordings

Attempts have been made by Kjellberg et al (1950) to study variations in pulmonary blood-flow by recording lung-density variations, using an electrokymographic method described by Engstrom et al (1949) Marchal et al (1946, 1949, 1959) have studied lung-density variation during respiration, paying particular attention to the pulsation of the pulmonary arteries These authors have also found that the variation in density of each lung during respiration correlates well with bronchospirometric findings Other workers (Simonin et al 1950, 1951) have attempted to study lung function by photometric comparison of the film densities on inspiration and expiration of similar areas of lung, radiographed through a kymographic grid They have compared this method with electrokymographic measurements of lung density, and compared both methods with bronchospirometry

Methods

Description of Apparatus

The apparatus is illustrated in figs 1a and b

The image of the lung field, formed on the phosphor of a 5-in Philips image-intensifier, is viewed through a binocular eyepiece to establish the exact area under examination A photomultiplier (R C A type 913) in a special mounting is substituted for the eyepiece An iris diaphragm is fitted to the

mortality-rate was likewise three times greater in this group

Comment

These data support those of Morris (Morris et al 1953, Morris and Crawford 1958) indicating the preventive influence of bodily activity

Jewish people are reputedly especially prone to ischæmic heart-disease (Epstein et al 1957), but our findings do not support this belief The annual incidence of myocardial infarction among the sedentary Jewish workers whom we studied is almost identical with that in London sedentary workers observed by Morris et al (1953) On the other hand, the incidence of myocardial infarction among non-sedentary workers in Kibbutz (0 8 per 1000 men per year) is only half the incidence among London postmen who walked in their daily work (1 6 per 1000 men per year)

These findings underline the importance of physical exercise as a factor in the prevention of myocardial infarction

This research was carried out with the aid of a grant from the Fund for Applied Research of the Israeli Ministry of Health and from the Research Foundation of the General Federation of Jewish Labour in Israel (Histadruth)

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patient Fig 1 illustrates our technique, using a dialyser with 18 m of cellophane tubing

The perforated metal cylinders which form the screens for the cellophane spiral must be reinforced by a metal " skeleton " The inner cylinder would otherwise be damaged during operation by the considerable pressure resulting from application of positive pressure over a large surface Blood is pumped from the patient by a ' Sigma ' finger pump with adjustable speed (fig 1, P) The pump can be adjusted to ' occlusive " setting, which makes the rate of blood-flow relatively independent of the pressure head in A A is a simple manometer system which records the blood-pressure before it enters the proximal cellophane coils S is the cellophane spiral where ultrafiltration takes place This spiral is immersed in bath fluid B is a manometer system which records the blood-pressure as it leaves the distal coils The outflow tube can be narrowed by an adjustable screw, K, whereupon the pressure in B and in A will increase By using manometers A and B various pressure-flow relations can be recorded, this system also allows the blood flow-rate to be measured in vitro

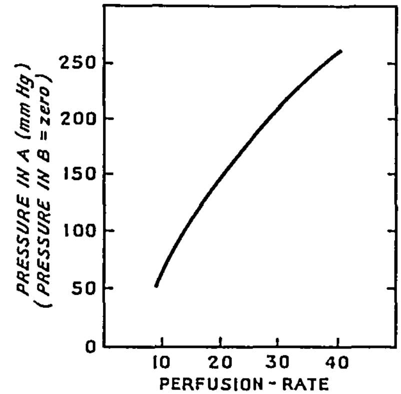

Fig 2—Pressure-flow relations in ultrafiltration with an 18 m cellophane tube, and without constriction of outflow tube

The pressure in A reaches 200 mm Hg at a perfusion-rate of 30 litres per hour

Fig 2 shows the increase in pressure in A when the rate of flow is increased without raising the pressure in B by creating a resistance at K As maximum safe pressure we have empirically chosen 200 mm Hg Above this pressure the inner cylinder may be damaged (even when reinforced) or the cellophane tube may leak 200 mm Hg pressure in A is achieved with a flow-rate of 30 litres per hour

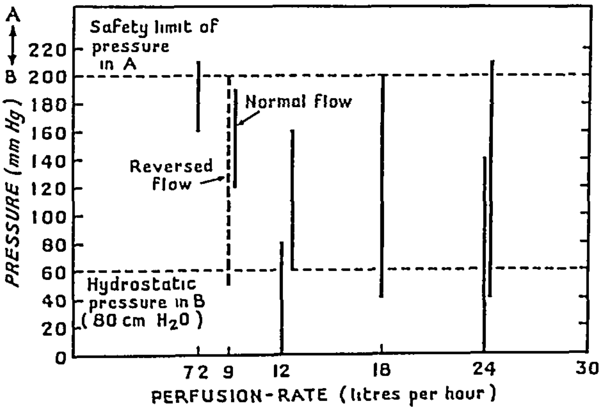

Fig 3—Pressure-flow relations with an 18 m cellophane ultrafiltrator

Pressure at B is variably increased Only moderate perfusion rates allow the pressure at B to increase considerably without excessive increase at A

Fig 3 shows the pressure-flow relations if the resistance at R is increased Each vertical column represents at the top the pressure in A, and at the bottom the pressure in B, at a certain flow-rate High flow-rates do not permit high pressures in B, because the pressure in A would then pass the safety limit Ultrafiltration will be most efficient, however, if it takes place along the whole length of the cellophane tubing, and for this a high pressure is necessary in B This can only be obtained with a moderate perfusion-rate Too low a rate is unfavourable because the blood becomes excessively dehydrated, and ultra filtration is handicapped by increasing colloid-osmotic pressure A moderate flow of 10–12 litres per hour seems to be best for ultrafiltration If the direction of blood-flow is reversed (from below upwards) the pressure difference between A and B increases considerably because the hydrostatic pressure of the bath fluid has now to be overcome at A The resulting mean pressure $\frac{(A+B)}{2}$ is lower than with a normal flow, hence the direction of the blood-stream should be downwards

The efficiency of dialysis is greater if the flow-rate is increased (fig 4) High perfusion-rates (20–30 litres per hour) result in rapid clearances and consequently short dialyses If dialysis is combined with ultrafiltration, however, moderate flows of 10–12 litres per hour seem preferable

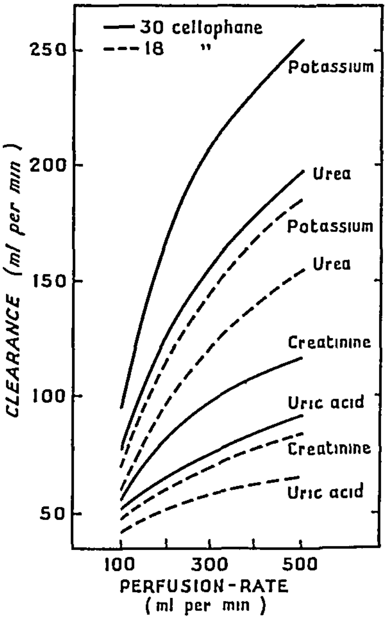

Fig 4—In-vitro clearances of the Alwall kidney at different perfusion-rates

We observed in vitro a water extraction of about 300 ml per hour—a figure which correlates well with our clinical experience and with other published data Higher rates of dehydration may lead to shock and hypotension The above rate was well tolerated by overhydrated patients, and it did not cause hypotension, although hypertension was sometimes reduced to normal

Summary

The artificial kidney of the Alwall type can be used for controlled ultrafiltration by creating a pressure difference between the extracorporeally circulating blood and the bath fluid

The optimal flow-rate for ultrafiltration is lower than that for dialysis

In clinical ultrafiltration water extraction of 300 ml per hour did not lead to hypotension if the patient was overhydrated

STAPHYLOCOCCAL PNEUMONIA IN THE NEONATAL PERIOD

R L EDWARDS
M B Lond , M R C O G
ELMORE STUDENT, UNIVERSITY OF CAMBRIDGE

G A GRESHAM
M A , M D Cantab
UNIVERSITY LECTURER IN PATHOLOGY

THE DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAMBRIDGE

THE pattern of tissue reaction to microbial infection varies with the virulence of the organism, the resistance of the host, and occasionally with the portal by which the organism gains access Neonatal lung infection with the staphylococcus illustrates this point

We describe here eight examples of staphylococcal pneumonia in the neonate which occurred during the period March, 1958, to August, 1959 They illustrate the often fulminant character of the infection and the variety of histological appearances in the lungs, and emphasise the need for the diligent use of the aseptic method in the care of the newly born

Illustrative Case-record

Stillborn infant, aged 39 weeks The mother, a multipara aged 31, was admitted with toxæmia on Aug 5, 1959, at 37th week of pregnancy She was kept in bed, but her hypertension did not lessen and it was decided to induce labour by hind-water rupture of the membranes, this was done on Aug 14 The next day an oxytocin (' Pitocin ') drip was given which induced uterine contractions

The temperature rose to 105°F on the following day, with a rigor, tenderness was noted in the right loin and right iliac fossa A diagnosis of pyelitis of pregnancy was made, urine examination showed a few pus cells, and *Proteus vulgaris* was cultured A high vaginal swab produced a growth of *Staphylococcus pyogenes*, sensitive to most antibiotics, the organism was not present in the patient's nose Benzyl penicillin (penicillin G) 500,000 units and streptomycin 0 5 g were given twice daily On the same day, when the cervix was two finger breadths dilated, at approximately 1 30 P M , the fœtal heart sounds became inaudible

She was delivered at 3 45 P M on Aug 16 of a stillborn male fœtus weighing 5¹/₄ lb (2410 g) Her temperature became normal next day, and recovery was uneventful

Necropsy

Tiny hæmorrhages were scattered over the visceral pleuræ of both lungs and over the visceral pericardium Small quantities of blood-stained fluid were seen in both pleural and pericardial cavities The spleen weighed 14 g , and appeared normal

No other abnormality was found The placenta and umbilical cord appeared normal macroscopically

Histological Findings

Lungs —All lobes of the lungs contained areas of intra-alveolar hæmorrhage, mingled with clusters of polymorphonuclear leucocytes and clumps of staphylococci There were numerous epithelial squames in alveoli and alveolar ducts A few veins contained thrombi

Placenta —Areas of purulent infiltration were seen in sections of placenta and umbilical cord

Bacteriological Investigations

The lungs and spleen were examined by the method described by Gresham and Gleeson-White (1957) All lobes grew a strain of *Staph pyogenes*, sensitive to all antibiotics against which it was tested (case 8, table III) The spleen was sterile

The findings in the other cases in this series are summarised in table I

Discussion

All infants showed histological evidence of pneumonia which varied from predominantly hæmorrhagic to frankly purulent infiltration In every case *Staph pyogenes* was isolated from the lungs

The histological appearances in the lungs could be classified broadly into three main groups

1 Extensive intra-alveolar hæmorrhage with necrosis of alveolar walls, together with abundant staphylococci Polymorphonuclear leucocytic infiltration was scanty This appears to represent an overwhelming infection—the organism being at the peak of its virulence and the host resistance low Two cases (1 and 6) fall into this group

2 Five showed the usual appearances of bacterial bronchopneumonia with sparse intrapulmonary hæmorrhage The duration of illness in these cases (3–7) was of the order of days rather than hours, as in the first group

3 One showed sparse polymorphonuclear leucocytic infiltration in alveoli (case 2) The staphylococcus was isolated both from the lung and from the spleen The changes in the lungs reflected those seen in other organs and were due to septicæmia

Five cases were infected with *Staph pyogenes* of the same antibiotic resistance patterns as those of the indigenous hospital staphylococcus This suggested that the source of infection was the hospital environment The route of infection in at least four of these was probably vaginal, three showed placentitis on histological examination In one (case 7) the infant was delivered at another hospital and the placenta was not available Nevertheless, the mother's vagina contained a *Staph pyogenes* similar in antibiotic resistance pattern to that isolated from the fœtal lung The finding of placentitis strongly supports the view that the bronchopneumonia in the fœtus was due to inhalation of infected amniotic fluid Further evidence

TABLE I—CLINICAL FEATURES

Case no	Antenatal history	Duration of pregnancy in weeks	Delivery	Stillbirth or neonatal death	History of infant	Duration of life
1	Essential hypertension toxæmia P.R.M	31	Normal	N N.D	Neonatal asphyxia intragastric oxygen	42 hours
2	5 threatened abortions P.R.M	30	Normal fœtal distress	N N.D	Neonatal asphyxia intragastric oxygen	37 hours
3	2 false labours	42	Normal fœtal distress	N.N.D	Neonatal asphyxia intragastric oxygen	4 days
4	Emergency admission at full dilatation	36	Normal	N N D	Not intubated	11 days
5	Toxæmia P.R M	38	Normal	N.N D	Not intubated	18 days
6	Eclampsia P R.M	33	Cæsarean section	N N.D	Not intubated oxygen by positive-pressure mask	36 hours
8	Toxæmia A R.M	39	Oxytocin drip rigors during labour temp 105 F fœtal distress N D	S.B	Not available	Not known

P.R.M =premature rupture of membranes A.R.M =artificial rupture of membranes S.B =stillbirth N.N D =neonatal death N.D =normal delivery

Analysis of the density curves is concerned with (1) the amplitude of the density variation in relation to the spirometer tracings, and (2) alterations in the time relationship between the two tracings

To illustrate these points two examples are described

Case 1 *Pulmonary emphysema with bullous emphysema of the right lower zone*—The spirometer tracings were similar during the examination of each of the four areas Normal respiration with a tidal flow of 1000–1200 ml of air was followed by a full inspiration (held for approximately 5 sec) and finally the forced expiration of approximately 2000 ml of air The forced expiration was considerably slower than in the normal subject (fig 6)

In the areas examined, the density tracings show considerable differences in amplitude and timing The left lower-zone tracing appears almost normal, following the spirometer curve closely The curve is synchronous with the spirometer tracing and the only abnormality is that, on forced expiration, the rate of loss of density is less than in the normal In the left upper-zone tracings, on forced expiration, there is a rapid initial loss of density, followed by a sudden check, and then a more gradual loss of density This contrasts with the smooth curve obtained from the lower zone The density tracing in the right upper zone is similar on forced expiration, but there is very little variation in lung density on normal respiration The density tracing in the right lower zone is grossly abnormal The density and spirometer curves are completely out of phase During respiration, the lung becomes more dense on inspiration and less dense on expiration On forced expiration, the lung initially becomes a little less dense and then shows no further change, even though the spirometer curve indicates that air is being expired from the lungs as a whole

Comment—The left lower zone is the area in which the tracings are nearest to normal There is the good synchronous variation in density with respiration, and an even loss of density on forced expiration This suggests that the most useful air movement is taking place in this area of the lung The upper zones, by comparison, show little variation in density on respiration On forced expiration, the sudden check in the density curve suggests that there is partial air-trapping after the start of expiration

The curves in the right lower zone are paradoxical, the density curve shows brightening on expiration The explanation for this is not known, but it may be due to air movement within the lungs, the air flowing into this region from other parts of the lungs

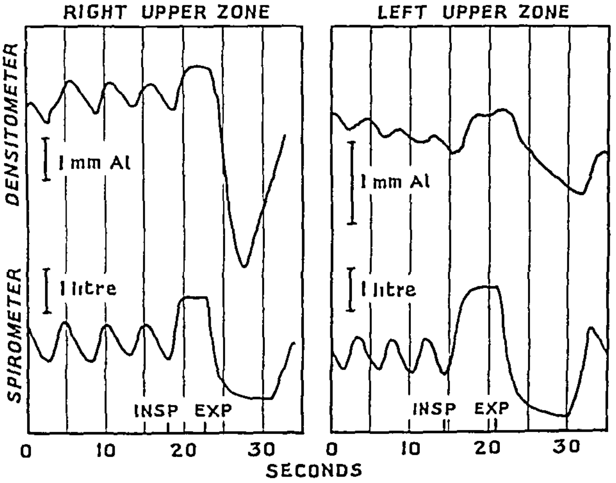

Fig 7—Case 2 Unilateral hypertranslucency of the left lung

The most important features are the smaller amplitude of density change on respiration and the slower rate of loss of density on forced expiration of the left upper zone compared with the right Since the densitometer sensitivity was greater when the left recording was made, the difference between the two sides is greater than appears at first sight

Case 2 *Radiological translucency of one lung*—A young man, without symptoms, was found, on routine X-ray examination, to have unilateral hypertranslucency of the left lung (Macleod 1954) The right pulmonary arteries appeared normal but the left pulmonary arteries appeared abnormally small Fluoroscopic examination showed that on expiration the left lung failed to deflate fully and the mediastinum swung to the right

The tracings obtained for the right and left upper zones are shown in fig 7 The spirometer tracings were similar when the two areas were examined The density and spirometer curves show synchronous movement But on normal respiration there is a much smaller amplitude of density change in the left upper zone when compared with the right On forced expiration, there is a much slower rate of loss of density in the left than in the right lung Similar changes were found in other zones It should be noted that the densitometer sensitivity was greater when recording the left side than when recording the right side (see scale fig 7), which means that the actual difference in density is greater than appears on the graphs

Comment—The small variation in lung density on normal respiration and the slow loss of density on forced expiration probably indicate that there is a much reduced air flow into and out of the left lung when compared with the right

Discussion

A number of factors, pulmonary and extrapulmonary, influence the overall radiolucency of the lung-fields during respiration The extrapulmonary factors are the ribs and soft tissues of the thoracic cage Their influence on the density curves is small On inspiration, the girth of the thoracic cage increases, thinning the overlying soft tissues and making them slightly more radiolucent This change is in phase with and slightly augments the overall pulmonary density curve The change in density caused by the ribs moving across the field during respiration is less regular than the soft-tissue effect By choosing a 5 cm diameter field, it is possible to even out the density changes produced by the ribs For example, the effect of the ribs and soft tissues over a pneumothorax, when no lung is in the field, is small compared with the changes in density over a normal lung field

The variation in radiolucency attributable to the pulmonary components are due to changes in blood contents and changes in air contents, the vascular component causes only a small ripple on the relatively large pulmonary density curve The main density changes are due to the air component

Sokolov (1956) has shown, by inflating the lungs of cadavers under experimental conditions, that the decrease in density which occurs with pulmonary inflation is dependent upon the total amount of lung tissue through which the X rays pass, and that this depends mainly on the amount of lung expansion which takes place in directions perpendicular to the rays Thus, in an anterior view of a lung, the decrease in density is influenced mainly by expansion in the vertical and transverse directions, in the coronal plane, and only little by expansion in the anteroposterior direction

The alterations of lung density during respiration, recorded by our densitometer, are a function of the degree of expansion of the part of lung under observation, and hence of the amount of air exchanged Since the observations are carried out under dynamic conditions, the curves give some indication of the air flow into and out of this part of the lung There is a recognisable normal pattern of tracings in different parts of the lung fields When there are abnormalities, correlation of the density tracings in the different areas with the spirometer tracings allows one to detect abnormalities of air flow When alterations in lung density occur without spirometer movement, intrapulmonary air flow must be taking place When there is localised air trapping, the densitometer tracing may show a slow rate of loss of density even though the spirometer tracings may be relatively normal Normally the densitometer and spirometer tracings are synchronous Asynchronous curves imply localised air-flow obstruction, or even reversal, as in one of our cases

The place of this radiological technique in the study of lung function has not yet been fully assessed It is hoped to correlate this method with other more conventional lung-function tests in order to establish its clinical value as a routine procedure

Summary

A radiological method of studying localised changes in lung density during respiration is described Simultaneous spirometer recordings are made

The curves obtained in normal and abnormal patients are described and analysed

The significance and interpretation of these findings is discussed

We wish to thank Mr C R. Brecknell for the figures, and Dr G C. Rivett for allowing us to carry out density studies on case 2

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OPTIMAL PERFUSION-RATE IN HÆMODIALYSIS COMBINED WITH ULTRAFILTRATION

E E Twiss
M.D Amsterdam

M M P Paulssen
Ph D Amsterdam

DIALYSIS DEPARTMENT, ST CLARA HOSPITAL, ROTTERDAM, THE NETHERLANDS

In acute renal insufficiency patients not infrequently become overhydrated as water is liberated from the cells by catabolic processes Water is also formed by oxidation of body fat and dextrose To prevent overhydration the intake of water must be rigorously restricted (to 400–500 ml per day) during the anuric phase Overhydration may lead to pulmonary œdema and bronchopulmonary infection, and cerebral œdema sometimes causes convulsions, especially when too much sodium has been given in an attempt to correct acidosis

If progressive uræmia is complicated by severe overhydration, treatment with combined hæmodialysis and ultrafiltration is indicated Ultrafiltration occurs if the pressure in the extracorporeally circulating blood (i e, the colloid-osmotic pressure of the plasma) is at least 30 mm Hg higher than the pressure in the surrounding bath fluid, this is technically feasible only if the filter membrane (' Cellophane ') is supported by a rigid screen which prevents changes of the extracorporeal blood-volume Kolff's rotating kidney lacks this support, and therefore cannot be used as an ultrafiltrator Kolff's twin-coil kidney, however, is supported, in this type of kidney ultrafiltration is obligatory because the high inner resistance of the narrow cellophane coils demands a high perfusion pressure But the Skegg-Leonards and Alwall types of kidney seem preferable because they both give support to the cellophane membrane and allow controlled ultrafiltration

Method

In our department a modified Alwall dialyser has been used since 1952 Under standard conditions the patient loses no water As the inner resistance of the cellophane tubing spiral is low, a moderate perfusion pressure suffices for satisfactory flow This slight " over " pressure is partially compensated by the colloid-osmotic pressure and partially by the hydrostatic pressure of the bath fluid If the direction of flow through the cellophane spiral is from above downwards, the proximal coils will cause some ultrafiltration because the blood-pressure is high and the hydrostatic pressure of the bath fluid is low The distal coils will take up water from the bath because the perfusion pressure is low and the hydrostatic pressure of the bath is high In practice this maintains the water balance, as is shown by weighing the patient with a bed scale before, during, and after dialysis The bath fluid we use is not hypertonic to uræmic plasma

Ultrafiltration is made possible by placing an airtight lid on the bath-fluid reservoir, so creating a negative pressure in the air above the bath fluid The hydrostatic pressure in the bath will thus be lowered, and a pressure gradient will be established between bath fluid and blood This method has several disadvantages, including the high cost of airtight apparatus, the maintenance of a constant vacuum, and the sudden changes in blood-volume which arise during the rapid creation of a vacuum (although these changes are limited by the screen support, they may disturb the patient) A much simpler, cheaper, and easier way is to raise the pressure of the circulating blood This can be done by using a higher perfusion-rate, and by increasing the resistance in the circuit by constricting the outflow tube from the " kidney " to the

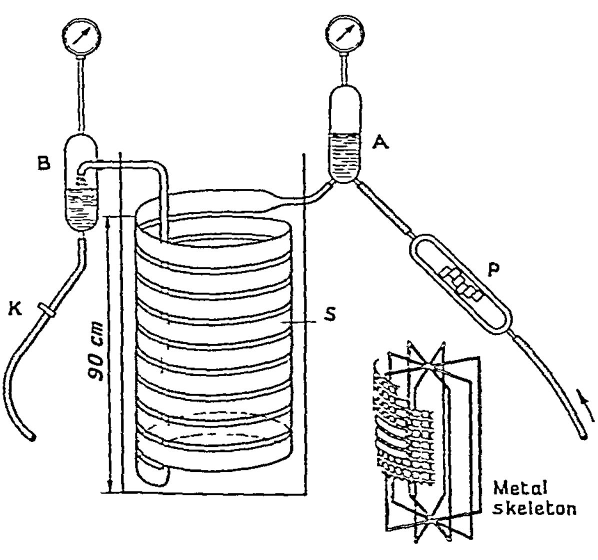

Fig 1—Schematic drawing of the Alwall kidney as ultrafiltrator P=finger pump A and B=manometers respectively proximal and distal to the cellophane spiral, S K=adjustable screw

patient Fig 1 illustrates our technique, using a dialyser with 18 m of cellophane tubing

The perforated metal cylinders which form the screens for the cellophane spiral must be reinforced by a metal " skeleton " The inner cylinder would otherwise be damaged during operation by the considerable pressure resulting from application of positive pressure over a large surface Blood is pumped from the patient by a ' Sigma ' finger pump with adjustable speed (fig 1, P) The pump can be adjusted to ' occlusive " setting, which makes the rate of blood-flow relatively independent of the pressure head in A A is a simple manometer system which records the blood-pressure before it enters the proximal cellophane coils S is the cellophane spiral where ultrafiltration takes place This spiral is immersed in bath fluid B is a manometer system which records the blood-pressure as it leaves the distal coils The outflow tube can be narrowed by an adjustable screw, K, whereupon the pressure in B and in A will increase By using manometers A and B various pressure-flow relations can be recorded, this system also allows the blood flow-rate to be measured in vitro

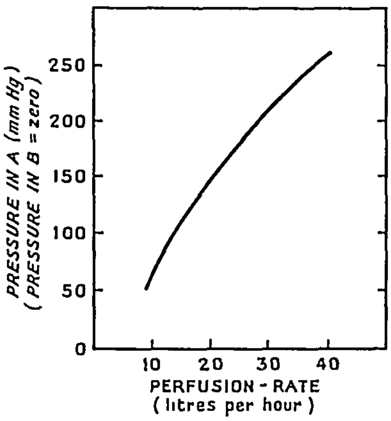

Fig 2—Pressure-flow relations in ultrafiltration with an 18 m cellophane tube, and without constriction of outflow tube

The pressure in A reaches 200 mm Hg at a perfusion-rate of 30 litres per hour

Fig 2 shows the increase in pressure in A when the rate of flow is increased without raising the pressure in B by creating a resistance at K As maximum safe pressure we have empirically chosen 200 mm Hg Above this pressure the inner cylinder may be damaged (even when reinforced) or the cellophane tube may leak 200 mm Hg pressure in A is achieved with a flow-rate of 30 litres per hour

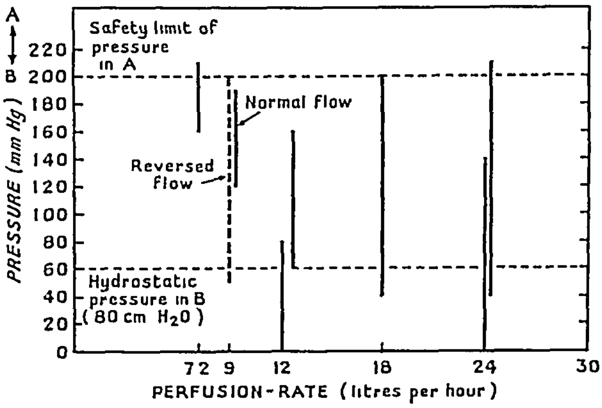

Fig 3—Pressure-flow relations with an 18 m cellophane ultrafiltrator

Pressure at B is variably increased Only moderate perfusion rates allow the pressure at B to increase considerably without excessive increase at A

Fig 3 shows the pressure-flow relations if the resistance at R is increased Each vertical column represents at the top the pressure in A, and at the bottom the pressure in B, at a certain flow-rate High flow-rates do not permit high pressures in B, because the pressure in A would then pass the safety limit Ultrafiltration will be most efficient, however, if it takes place along the whole length of the cellophane tubing, and for this a high pressure is necessary in B This can only be obtained with a moderate perfusion-rate Too low a rate is unfavourable because the blood becomes excessively dehydrated, and ultrafiltration is handicapped by increasing colloid-osmotic pressure A moderate flow of 10–12 litres per hour seems to be best for ultrafiltration If the direction of blood-flow is reversed (from below upwards) the pressure difference between A and B increases considerably because the hydrostatic pressure of the bath fluid has now to be overcome at A The resulting mean pressure $\frac{(A+B)}{2}$ is lower than with a normal flow, hence the direction of the blood-stream should be downwards

The efficiency of dialysis is greater if the flow-rate is increased (fig 4) High perfusion-rates (20–30 litres per hour) result in rapid clearances and consequently short dialyses If dialysis is combined with ultrafiltration, however, moderate flows of 10–12 litres per hour seem preferable

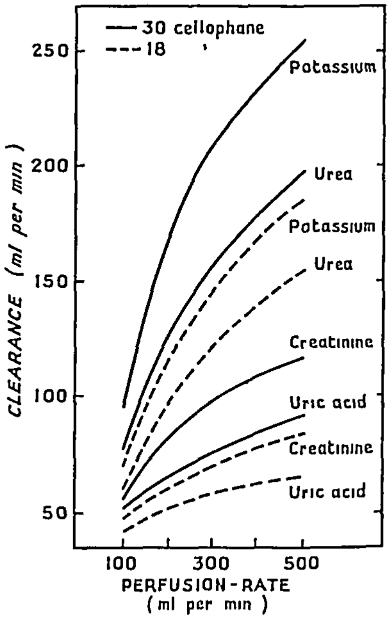

Fig 4—In-vitro clearances of the Alwall kidney at different perfusion-rates

We observed in vitro a water extraction of about 300 ml per hour—a figure which correlates well with our clinical experience and with other published data Higher rates of dehydration may lead to shock and hypotension The above rate was well tolerated by overhydrated patients, and it did not cause hypotension, although hypertension was sometimes reduced to normal

Summary

The artificial kidney of the Alwall type can be used for controlled ultrafiltration by creating a pressure difference between the extracorporeally circulating blood and the bath fluid

The optimal flow-rate for ultrafiltration is lower than that for dialysis

In clinical ultrafiltration water extraction of 300 ml per hour did not lead to hypotension if the patient was overhydrated

STAPHYLOCOCCAL PNEUMONIA IN THE NEONATAL PERIOD

R. L. Edwards
M.B Lond., M.R.C.O.G
ELMORE STUDENT, UNIVERSITY OF CAMBRIDGE

G. A. Gresham
M.A., M.D Cantab
UNIVERSITY LECTURER IN PATHOLOGY

THE DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAMBRIDGE

THE pattern of tissue reaction to microbial infection varies with the virulence of the organism, the resistance of the host, and occasionally with the portal by which the organism gains access Neonatal lung infection with the staphylococcus illustrates this point.

We describe here eight examples of staphylococcal pneumonia in the neonate which occurred during the period March, 1958, to August, 1959 They illustrate the often fulminant character of the infection and the variety of histological appearances in the lungs, and emphasise the need for the diligent use of the aseptic method in the care of the newly born.

Illustrative Case-record

Stillborn infant, aged 39 weeks The mother, a multipara aged 31, was admitted with toxæmia on Aug 5, 1959, at 37th week of pregnancy She was kept in bed, but her hypertension did not lessen and it was decided to induce labour by hind-water rupture of the membranes, this was done on Aug 14. The next day an oxytocin ('Pitocin') drip was given which induced uterine contractions

The temperature rose to 105°F on the following day, with a rigor, tenderness was noted in the right loin and right iliac fossa. A diagnosis of pyelitis of pregnancy was made, urine examination showed a few pus cells, and *Proteus vulgaris* was cultured A high vaginal swab produced a growth of *Staphylococcus pyogenes*, sensitive to most antibiotics, the organism was not present in the patient's nose Benzyl penicillin (penicillin G) 500,000 units and streptomycin 0 5 g were given twice daily On the same day, when the cervix was two finger breadths dilated, at approximately 1.30 P.M., the fœtal heart sounds became inaudible.

She was delivered at 3 45 P M. on Aug 16 of a stillborn male fœtus weighing 5¹/₄ lb (2410 g) Her temperature became normal next day, and recovery was uneventful.

Necropsy

Tiny hæmorrhages were scattered over the visceral pleuræ of both lungs and over the visceral pericardium. Small quantities of blood-stained fluid were seen in both pleural and pericardial cavities The spleen weighed 14 g, and appeared normal.

No other abnormality was found. The placenta and umbilical cord appeared normal macroscopically

Histological Findings

Lungs.—All lobes of the lungs contained areas of intra-alveolar hæmorrhage, mingled with clusters of polymorphonuclear leucocytes and clumps of staphylococci. There were numerous epithelial squames in alveoli and alveolar ducts A few veins contained thrombi.

Placenta.—Areas of purulent infiltration were seen in sections of placenta and umbilical cord.

Bacteriological Investigations

The lungs and spleen were examined by the method described by Gresham and Gleeson-White (1957) All lobes grew a strain of *Staph pyogenes*, sensitive to all antibiotics against which it was tested (case 8, table III) The spleen was sterile

The findings in the other cases in this series are summarised in table I

Discussion

All infants showed histological evidence of pneumonia which varied from predominantly hæmorrhagic to frankly purulent infiltration. In every case *Staph pyogenes* was isolated from the lungs

The histological appearances in the lungs could be classified broadly into three main groups

1 Extensive intra-alveolar hæmorrhage with necrosis of alveolar walls, together with abundant staphylococci Polymorphonuclear leucocytic infiltration was scanty This appears to represent an overwhelming infection—the organism being at the peak of its virulence and the host resistance low Two cases (1 and 6) fall into this group

2 Five showed the usual appearances of bacterial bronchopneumonia with sparse intrapulmonary hæmorrhage The duration of illness in these cases (3–7) was of the order of days rather than hours, as in the first group

3 One showed sparse polymorphonuclear leucocytic infiltration in alveoli (case 2) The staphylococcus was isolated both from the lung and from the spleen. The changes in the lungs reflected those seen in other organs and were due to septicæmia

Five cases were infected with *Staph pyogenes* of the same antibiotic resistance patterns as those of the indigenous hospital staphylococcus This suggested that the source of infection was the hospital environment. The route of infection in at least four of these was probably vaginal, three showed placentitis on histological examination In one (case 7) the infant was delivered at another hospital and the placenta was not available Nevertheless, the mother's vagina contained a *Staph pyogenes* similar in antibiotic resistance pattern to that isolated from the fœtal lung The finding of placentitis strongly supports the view that the bronchopneumonia in the fœtus was due to inhalation of infected amniotic fluid. Further evidence

TABLE I—CLINICAL FEATURES

Case no	Antenatal history	Duration of pregnancy in weeks	Delivery	Stillbirth or neonatal death	History of infant	Duration of life
1	Essential hypertension toxæmia. P.R.M.	31	Normal	N.N.D	Neonatal asphyxia intragastric oxygen	42 hours
2	5 threatened abortions. P.R.M.	30	Normal foetal distress	N.N.D	Neonatal asphyxia intragastric oxygen	37 hours
3	2 false labours	42	Normal foetal distress	N.N.D	Neonatal asphyxia, intragastric oxygen	4 days
4	Emergency admission at full dilatation	36	Normal	N.N.D	Not intubated	11 days
5	Toxæmia. P.R.M.	38	Normal	N.N.D	Not intubated	18 days
6	Eclampsia. P.R.M.	33	Cæsarean section	N.N.D	Not intubated, oxygen by positive-pressure mask	36 hours
8	Toxæmia. A.R.M.	39	Oxytocin drip rigors during labour temp 105 F foetal distress N.D	S.B.	Not available	Not known

P.R.M. = premature rupture of membranes A.R.M. = artificial rupture of membranes S.B. = stillbirth N.N.D = neonatal death N.D = normal delivery

TABLE II—PATHOLOGY

Case no	Weight (g)	Ossification centres	Lung	Œsophagus	Other organs	Placenta
1	1320	c	Lung hæmorrhage, pneumonia, squames ±	Œsophagitis	Normal	No inflammatory changes
2	955	c, Ta	Pneumonia, squames ++	Œsophagitis	Normal	Inflammatory reaction in placenta and cord
3	1397	c, Ta	Bronchopneumonia, squames ++	Œsophagitis	Normal	Inflammatory reaction in placenta and cord
4	2270	c, Ta, F	Bronchopneumonia, no squames	Normal	Meningitis, hydrocephalus, meningomyelocele, spina bifida, C D H	No infection
5	1620	c, Ta, F, Ti	Bronchopneumonia, no squames	Normal	Meningitis, pericarditis microcephaly, proptosis, spina bifida	Not available
6	1122	c, Ta	Lung hæmorrhage, broncho pneumonia, squames ±	Normal	Normal	No infection
7	1055	c, Ta	Bronchopneumonia, squames ++	Normal	Staphylococcal enteritis	Not available
8	2410	c, Ta, F	Bronchopneumonia, squames ++	Normal	Normal	Inflammatory reaction in placenta and cord placentitis

Ossification centres c=calcaneum Ta=talus, F=lower end of femur Ti= upper end of femur, cuboid
C D H =congenital dislocation of the hip ++=many, ±=few

TABLE III—BACTERIOLOGY

Case no	Interval from death to bacteriological examination	Bacteriological examination of infant							Bacteriological examination of mother							Interval from delivery to bacteriological examination
		Lung	Spleen	Sensitivity					Nose and Throat	Vagina	Sensitivity					
				Penicillin	Tetracycline	Erythromycin	Streptomycin	Chloramphenicol			Penicillin	Tetracycline	Erythromycin	Streptomycin	Chloramphenicol	
1	4 days	*Staph pyogenes*	Negative	R	S	S	S	S	Negative	Negative						5 days
2	3 days	*Staph pyogenes*	Positive	S	S	S	S	S	Negative	*Staph pyogenes*	S	S	S	S	S	2 days
3	2 days	*Staph pyogenes*	Negative	R	S	S	S	S	Negative	Negative						73 days
4	4 days	*Staph pyogenes*	Negative	R	S	S	S	S								Not made
5	2 days	*Staph pyogenes*	Negative	R	S	S	S	S								Not made
6	3 days	*Staph pyogenes*	Negative	S	S	S	S	S	Negative	Negative						5 days
7	6 days	*Staph pyogenes*	Negative	R	S	S/R	R	S	Negative	*Staph pyogenes*	R	S	S/R	R	S	2 days
8	2 days	*Staph pyogenes*	Negative	S	S	S	S	S	Negative	*Staph pyogenes*	S	S	S	S	S	Same day

S=sensitive R=resistant

for the view that inhalation was the route of pneumonic infection is provided by the occurrence of fœtal distress, and the presence of numerous amniotic squames in the air-passages of all infants in which this route is postulated A vaginal route of infection is also supported by the fact that an undue number of vaginal procedures were made in the antenatal period, these were carried out because of a high incidence of antenatal complications in these mothers (table I)

The sensitivity of the organisms to various antibiotics is shown in table III Three strains were sensitive to all the antibiotics against which they were tested These three organisms were probably derived from the mothers themselves, or from a newly introduced strain carried into the ward Case 8 (table I) is typical, a high vaginal swab from the mother before delivery showed a sensitive strain of *Staph pyogenes*

In three cases the mother's vagina did not grow *Staph pyogenes* though it was isolated from the fœtal lungs However, the interval of several days between delivery and taking a vaginal swab may explain this discrepancy

Cases 4 and 5 (table I) were infants with congenital abnormalities They survived much longer than all other infants in this series The organism responsible for their pneumonia had the same resistance pattern as the indigenous hospital staphylococcus They were probably infected post partum There were no inflammatory changes of the umbilical cord or placenta in case 4 The other placenta was not available

Three cases showed œsophagitis, associated with intubation and the administration of gastric oxygen The lesion was probably incidental, and was not the primary source of infection

All infants were premature as judged by weight The number of ossification centres found at necropsy varied from case to case (table III) Most were found in case 5—an infant with multiple congenital abnormalities This suggests that such babies may be expected to develop lung infections, either because prematurity reflects antenatal complications and the need for excessive manipulations, or because they are unduly susceptible to infection

Summary

Eight cases of fatal staphylococcal pneumonia in neonates are described The infection was often fulminant, and a variety of histological appearances—ranging from extensive intra-alveolar hæmorrhage with necrosis of the alveolar walls to a slight polymorphonuclear leucocytic infiltration—were found post mortem

The causal organism in every case was *Staphylococcus pyogenes* It is suggested that in six of the infants the bronchopneumonia was due to the inhalation of infected amniotic fluid, two cases were probably infected post partum The need for diligent application of aseptic methods in the care of the newly born is stressed

Our thanks are due to Dr A M Barrett, Dr D M T Gairdner, and Dr M H Gleeson-White for their cooperation in the preparation of this paper

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GONADAL DYSGENESIS (TURNER'S SYNDROME) WITH MALE PHENOTYPE AND XO CHROMOSOMAL CONSTITUTION

WALTER BLOISE
M.D. São Paulo

L. M. DE ASSIS
M.D. São Paulo

CASSIO BOTTURA
M.D. Ribeirão Preto

IRIS FERRARI
M.D. Ribeirão Preto

From the Department of Endocrinology and Metabolic Disorders, Faculty of Medicine, São Paulo, and the Department of Clinical Medicine, Faculty of Medicine, Ribeirão Preto, Brazil

A boy, aged 8, the eldest son of young parents, was admitted to the metabolic department on April 5, 1957, because of poor somatic development.

Maternal pregnancy and labour had been normal. General condition was fair. Height 3 ft. 9 in. (115 cm.), weight 45·4 lb. (20·6 kg.), span 3 ft. 7 in. (110 cm.) (fig. 1). Clinical examination revealed malformed external genitalia and some lesser congenital defects—low hair-line and ears, high-arched palate, and a number of naevi. The penis 1·2 in. (3·1 cm.) long, without urethral meatus, was bent ventrally by a web connecting the ventral surface to the perineum. Thus the "scrotum" appeared to be bifid, a depression with two small meatuses being visible in the midline, one communicated with the bladder through a short urethra, and the other led to a closed cavity (fig. 2). When the patient underwent plastic surgery, it was verified this cavity communicated with the uterus. No testes could be felt in the labioscrotal folds or in the inguinal regions. A rudimentary uterus was seen on peritoneoscopy and a laparotomy was done for further investigation of the internal genitalia. Near the small left tube was an elongated, almond-shaped mass $^3/_8$ in. (1 cm.) long, which was histologically a rudimentary testis (figs. 3 and 4). On the right, instead of an ovary, there was connective tissue, as seen in other cases of gonadal dysgenesis with negative chromatin pattern (Epps et al. 1958). 17-ketosteroids (Drekter) 0·8 mg. per 24 hours. Bone age of 7 years, X-ray examination of the skull, no abnormality. Colour-vision normal (Ishihara tests).

The nuclear sex in material obtained from the blood, oral smear, and from the skin biopsy was male. In the blood-smears, no "drumsticks" were found in 500 leucocytes counted. Chromosomal counts (Bottura and Ferrari 1960) in the 20 bone-marrow specimens examined gave a constant number of 45 chromosomes. In the 13 cells in optimal condition, 4 small acrocentric chromosomes could be positively identified. After pairing (fig. 5), the absence of a second medium-sized chromosome with subcentral centromere (probably an X chromosome) was noted. In view of these facts, the chromosomal constitution of the patient must be XO. The constancy of the number 45 in the chromosomal counts argues against

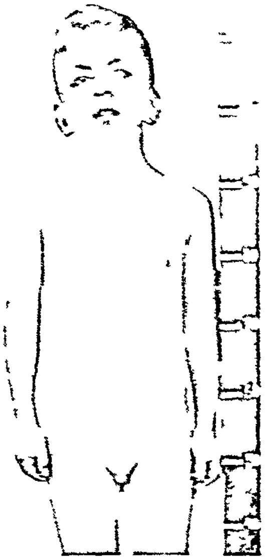

Fig. 1

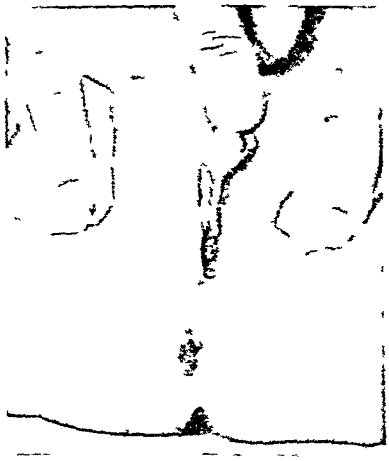

Fig. 2.

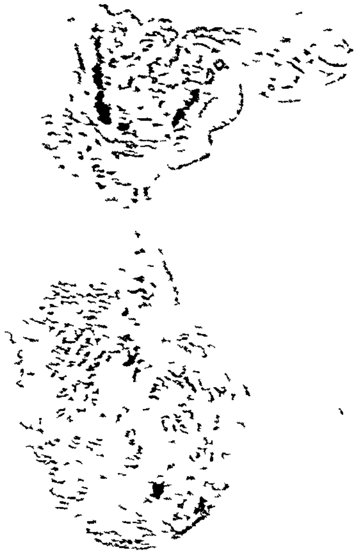

Fig. 3.

Fig. 1—Gonadal dysgenesis (Turner's syndrome) in a boy aged 8.

Fig. 2—The external genitalia.

Fig. 3—Embryonic testis.

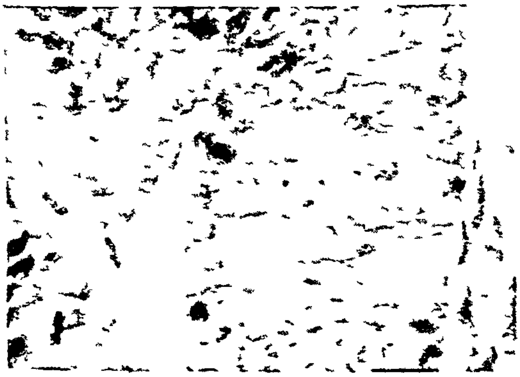

Fig. 4—Testicular tissue showing Sertoli cells, some undifferentiated germ cells, and spermatogonia. No later phases can be identified. Scanty and isolated interstitial cells are present. (Hæmatoxylin and eosin. × 220.)

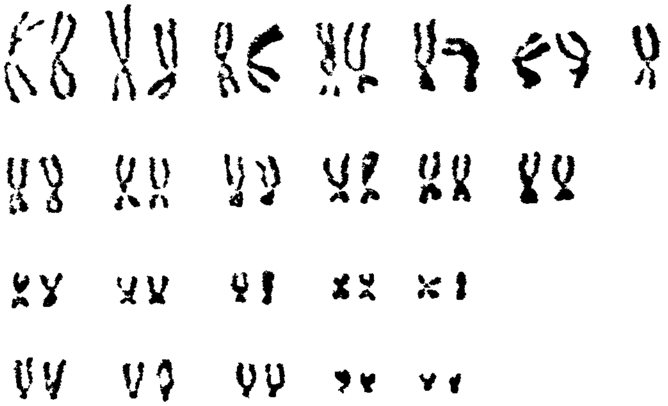

Fig. 5—Paired chromosomes from bone-marrow specimen showing absence of one X chromosome.

the possibility of mosaicism as far as bone-marrow cells are concerned

Discussion

XO chromosomal constitution in gonadal dysgenesis with female phenotype was described by Ford et al (1959) A reasonable assumption from the study of our case is that XO chromosomal constitution is not incompatible with a male phenotype and with the presence of embryonic testis Further instances of testicular development with a male phenotype without Y chromosome are represented by the XX true hermaphrodites recently reported (Harnden and Armstrong 1959, Hungerford et al 1959, de Assis et al 1960, Ferguson-Smith et al 1960)

Summary

We describe a case of gonadal dysgenesis (Turner's syndrome) in a boy of 8 He had a rudimentary uterus, and an embryonic testis No ovaries were found The nuclear sex was male " Drumsticks " were absent from the leucocytes Only 45 chromosomes were present in the cells of all (20) bone-marrow specimens examined, and chromosome analysis pointed to the absence of one X chromosome His phenotype is, therefore, male with an XO chromosomal constitution

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PREMEDICATION WITH ATROPINE BY MOUTH

M C Joseph
M D Cantab , M R C P , D C H
ASSISTANT TO THE DIRECTOR OF THE DEPARTMENT OF CHILD HEALTH

R J Vale
M B Lond , M R C P E , F F A R C S
CONSULTANT ANÆSTHETIST

GUY'S HOSPITAL, LONDON, S E 1

In 1872 Heidenhain demonstrated that the salivary secretion produced by stimulation of the chorda tympani was prevented by atropine, and, in the next year, Ebstein used it therapeutically in a patient with apoplexy In 1875 Munro reported its use in cats for preventing early cardiac arrest during chloroform anæsthesia, but it was not until after 1890 that the subcutaneous injection of atropine before induction of anæsthesia came into general use in this country

There seems to be no record of the oral administration of atropine before operation, though it is used therapeutically for various conditions Even when sedative drugs are given by mouth preoperatively, it has still been common practice to inject atropine, though Dr W S McConnell tells us he has used it by mouth effectively In children it is especially desirable to avoid injections, hence we conducted this trial of the effect of atropine given by mouth

The Trial

All children admitted to the Evelina Hospital, under the same surgeon and anæsthetist for tonsillectomy, were included in the trial When admitted, the day before the operation, the child was placed in an " oral " or " subcutaneous " group by random allocation, the anæsthetist being unaware of the grouping The trial lasted fifteen months, and ended when the anæsthetist ceased to work at this hospital

240 children were admitted to the trial, but 93 were excluded because a different anæsthetist was working on that occasion or because the data were incomplete There remained 147 children for study Their sex, average weights, and ages were

	No	*Males*	*Females*	*Age (yr)*	*Weight (lb)*
Oral	74	41	33	6 5	49
Subcutaneous	73	39	34	6 7	51

and the age-distribution was

	No	*3–5 yr*	*6–8 yr*	*9–12 yr*
Oral	74	21	44	9
Subcutaneous	73	17	15	11

The average interval between administration of atropine and induction of anæsthesia was 95 and 87 minutes for the oral and subcutaneous groups respectively

During the night before operation the sleeping pulse was measured twice Next morning, an hour before the expected time of operation, atropine was given—either 0 85 mg by mouth or 0 64 mg subcutaneously—with butobarbitone, in a dose of 75 mg per stone body-weight The pulse-rate was recorded again just before the child was taken to the operating-theatre, and the state of consciousness was noted In the anæsthetic-room the size of the pupils was measured to the nearest millimetre by comparison with a prepared scale, and the reaction to light was noted All patients were anæsthetised with ether after induction with either ethyl chloride on a Schimmelbusch mask or nitrous oxide and oxygen through a semiopen circuit The degree of salivation was assessed during induction by inserting a finger into the buccal sulcus, if it was dry or slightly moist, it was recorded as O, if wet but not dripping off the finger as +, and if copious and stringy as ++ Additionally, if salivation interfered with induction, it was recorded as ++

Results

Salivation

The degree of salivation was

	No	*O*	+	++
Oral	74	63	9	2
Subcutaneous	73	68	4	1

Excessive salivation was uncommon in either group, occurring only twice in the oral group and once in the subcutaneous group There was a little more mild salivation in the oral group than in the subcutaneous group, but the difference was small and not significant at the 5% level

Pupils

The average size of the pupils was identical in the two groups, and the incidence of negative reaction to light was similar

	No	*Size (mm)*	*Negative reaction*
Oral	74	6 1	15 (*19%*)
Subcutaneous	73	6 1	11 (*15%*)

Pulse-rate

The response of the pulse-rate was

	No	*Before atropine*	*After atropine*	*Rise*
Oral	74	85	107	22
Subcutaneous	73	86	111	25

The mean rate before atropine was similar in both groups, there being a rise of 22 and 25 beats per minute in the oral and subcutaneous groups respectively

Discussion

Dose

Unna et al (1950) have shown that the smallest effective dose of atropine for suppression of salivation in children aged 3–12 years is about 0 007 mg per kg body-weight subcutaneously, or three times this dose by mouth The dose for a 20 kg child is about a quarter the dose of

0 64 mg commonly used subcutaneously Mushin and Galloon (1953) also regard 0 64 mg subcutaneously as more than is needed to suppress salivation Thus our subcutaneous dose was probably three times larger than necessary, and our oral dose was the smallest effective dose recommended by Unna et al

Salivation

Although we evaluated the effect of atropine by several criteria, the suppression of salivation is especially important in premedication, and is also the most sensitive index of the effect of atropine (Unna et al 1950) Our finding of excessive salivation in 2% was similar to the 4% observed by Marx and Orkin (1959), but their figures were for atropine and scopolamine, and they pointed out that their atropine group had more secretion than their scopolamine group

During our study atropine was deliberately not given to a few patients, in order to establish that it had some effect But the excessive salivation and extreme bradycardia in the first five children so treated made us unwilling to continue, and we resumed the trial Mushin and Galloon (1953) pointed out that the degree of salivary depression necessary depended on the type of anæsthesia used, ether needing about 40% and nitrous oxide about 10% depression We used ether, and therefore our patients needed maximum depression of salivation

Pupils and Pulse-rate

Both mydriasis and tachycardia are unreliable signs of the effect of atropine, because anxiety, excitement, or barbiturates may also produce these signs, but atropine was probably responsible for mydriasis in some of our patients, as the correlation between size of pupil and reaction to light was significant

	No	*Size of pupil (mm) with positive reaction*	*No*	*Size of pupil (mm) with negative reaction*
Oral	59	5 7 ± 0 19	15	7 8 ± 0 82
Subcutaneous	62	5 8 ± 0 19	11	8 1 ± 0 96

Difference in size of pupils is significant ($P = < 0\ 05 > 0\ 02$)

We cannot be sure that the rise of pulse-rate was solely due to atropine, although it probably made a substantial contribution. The rise in pulse-rate was similar in both our groups

We were unable to show any correlation between pupil size, rise in pulse-rate, and salivation However, we found correlation between the size of pupil and its response to light, the fixed pupils having a mean diameter of 7 8 and 8 1 mm (oral and subcutaneous) compared with 5 7 and 5 8 mm for the active pupils It is interesting that we found this correlation in the oral group, for Unna et al (1950) pointed out that the smallest dose by mouth which suppressed salivation did not cause mydriasis or tachycardia

The average time between giving atropine and inducing anæsthesia was 95 and 87 minutes in the two groups This interval is similar to that observed by Unna et al (1950), who found the greatest effect of atropine was between sixty and a hundred and twenty minutes for an oral group, and to that of Mushin and Galloon (1953), who found the greatest effect between sixty and ninety minutes for a subcutaneous group

Our investigation has shown that, in children, atropine given by mouth is as effective as atropine given by subcutaneous injection As it is desirable to avoid injection in children, the oral route seems preferable

Summary

147 children randomly selected were given oral or subcutaneous atropine before anæsthesia, and the effects on salivation, pupils, pulse-rate, and anæsthesia were observed No differences between the groups were found

Thus is it concluded that atropine by mouth is satisfactory for premedication

We wish to thank the nursing staff and residents at the Evelina *Children's Hospital for their help, and Mr L F W Salmon for* allowing us to conduct this trial on patients under his care

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Preliminary Communications

ANTINUCLEAR FACTORS IN THE SERUM OF RELATIVES OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

DURING an investigation of antinuclear factors in the serum of patients with systemic lupus erythematosus (S L E) we found a relationship between the titre of antinuclear factors in the serum and the clinical activity of the disease High titres were found in patients with active S L E , the titres were considerably lower in most patients in whom the disease was adequately controlled by treatment with prednisone[1] As this test for antinuclear factors was sensitive, and as the results could be quantitated, we were prompted to examine the serum of relatives of patients with S L E for antinuclear factors, particularly in view of recent reports of the familial occurrence of S L E [2–8]

MATERIAL AND METHODS

Smears of fresh unfixed healthy human buccal mucosal epithelial cells were used as the source of the cell nuclei After washing with 0 01 *M* saline phosphate buffer (pH 7 0) the slides were air-dried, and the smears were covered with a drop of the test serum The smears were incubated for 90 minutes at room temperature in a moist atmosphere The slides were washed for 30 minutes in three changes of buffer, air-dried, and layered for 30 minutes with rabbit antihuman γ-globulin conjugated with fluorescein isothiocyanate (Sylvana) They were washed and were then mounted in buffered glycerin They were inspected for specific nuclear fluorescence, using a Reichert Zetopan microscope with an aplanatic dark field condensor (light source Osram HBO 200 mercury-vapour lamp, Corning 5840 and Wratten 2A filters)

All tests were done in duplicate When specific nuclear fluorescence was found, serial dilutions of serum (to 1 4096) were incubated with smears of buccal mucosal cells in a similar fashion The highest dilution in which specific nuclear fluorescence was detected was called the ' titre " of antinuclear factors

Full details of the technique and controls used will be published elsewhere[1] It was shown that duplicate titrations on the same sera gave identical titres in 4 of 10 instances The final titres differed by only one dilution in the other 6

RESULTS

The results are shown in table I Single serum samples from 40 healthy subjects and 50 sera from 45 patients with

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TABLE I—TITRES OF ANTINUCLEAR FACTORS IN HEALTHY SUBJECTS, IN PATIENTS WITH VARIOUS DISEASES UNRELATED TO S L E , AND IN PATIENTS WITH S L E AND THEIR RELATIVES

Titre of Antinuclear factors (dilution)	Healthy subjects	Diseases unrelated to S L E	Patients with S L E	Relatives of patients with S L E
Negative				
Undiluted	33	40	3	20
1:1	3	5	2	3
1:2	4	4	1	3
Positive				
1:4 to 1:16	0	1	12	17
1:32 to 1:128	0	0	14	4
1:256 to 1:4096	0	0	19	3

diseases unrelated to S L E were studied as controls Specific nuclear fluorescence was not seen with 73 of these sera, and was seen with undiluted serum or serum diluted 1:2 in another 16 sera In only 1 instance was specific nuclear fluorescence seen when the serum was diluted 1:4

51 patients with S L E were studied When the first serum drawn from each of these patients was examined, specific nuclear fluorescence was found with serum diluted 1:4 or higher in 45 In all, 151 specimens of serum from these 51 patients have been examined to date, and specific nuclear fluorescence with serum diluted 1:4 or higher was observed with 131 specimens As antinuclear factors were found when the serum was diluted 1:4 in only 1 of 90 sera examined as controls, the demonstration of antinuclear factors in serum diluted 1:4 or more appeared to distinguish patients with S L E from healthy subjects and those with a variety of other diseases The test was therefore called positive when antinuclear factors were demonstrated in serum diluted 1:4 or more

TABLE II—RESULTS OF TESTS FOR ANTINUCLEAR FACTORS IN THE RELATIVES OF PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Relationship	Female relatives		Male relatives	
	Positive tests	Negative tests	Positive tests	Negative tests
Parents	5	1	0	4
Siblings	6	4	4	5
Offspring	2	0	2	3
Maternal siblings	3	1	1	1
First cousins	1	0	0	1
Grandparents	0	3	0	3
Totals	17	9	7	17

Single serum samples from 50 members of families of 12 patients with S L E were studied (tables I and II) Specific nuclear fluorescence was demonstrated with serum diluted 1:4 or more in 24 instances Positive tests were found with the sera of 19 of 36 first-degree relatives tested, and with the sera of 5 of 14 second-degree relatives Positive tests were found in 17 of 26 female relatives but in only 7 of 24 male relatives The difference in the frequency of positive tests in male and female relatives is significant ($\chi^2 = 5{\cdot}2$, P = < 0·05), but further observations on this difference are necessary

Two family pedigrees are shown in fig

In the first pedigree the propositus (II 4) w a 15-year-old schoolgirl in whom defin clinical evidence of S L E had been found, an in the past, Hargraves' cells had been demonstrated in her blood Findings diagnostic o lupus nephritus were observed in a renal biops 4 specimens of serum were tested for antinuclear factors when the patient was symptom-free as a result of treatment with prednisone, all were negative Positive tests for antinuclear factors were found in the mother (I 1) and 3 of 5 siblings—in 1 of whom (II 1) the titre was 1:1024

In the second pedigree the propositus (II 2) was a 21-year-old American Negro housewife with typical S L E Positive tests for antinuclear factors were found in the serum of the patient, her 2 younger sisters, her 5-year-old son, and 3-year-old daughter (III 3)—in whom the titre of antinuclear factors was 1:4096

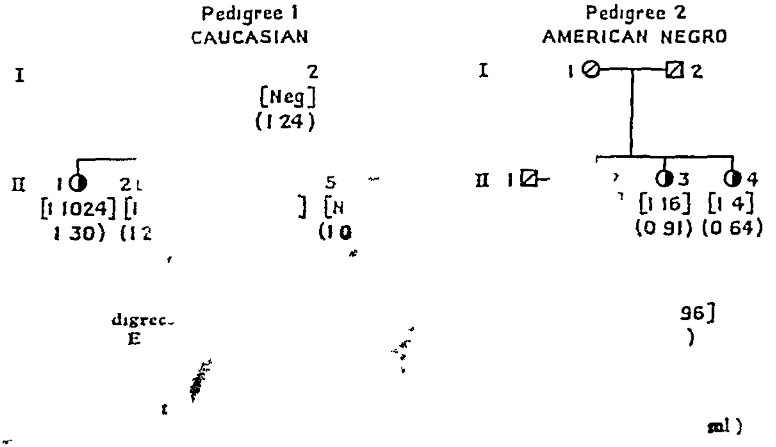
The serum-γ-globulin levels were estimated by the Biuret reagent and filterpaper electrophoresis They are compared in fig 2 with values from 62 healthy Caucasian (1·13±0·23 g per 100 ml) and 62 healthy American Negro subjects (1·37±0·30 g per 100 ml) Elevated γ-globulin levels (>2 S D above the mean of the controls) were found in only 3 Caucasian relatives and 2 Caucasian controls Decreased γ-globulin levels (>2 S D below the mean of the controls) were found in 1 Caucasian and 2 Negro relatives 5 of the 6 Negro relatives were members of one family (pedigree 2) The difference between the γ-globulin levels in the members of this family and those in the controls was significant ($\chi^2 = 17{\cdot}2$, P = < 0·01)

DISCUSSION

In 1957 Leonhardt [2] reported S L E in 3 of 14 siblings He pointed out that at that time there were only four reported instances of the familial occurrence of S L E

Subsequently, Agranat et al [3] Larsson and Leonhardt,[4] and Lawrence [5] have each reported S L E in 2 sisters Wagenhals and Burgeson [6] observed the disease in twin sisters Griffin et al [7] found S L E in a father and his daughter, and Holman and Deicher [8] reported its occurrence in a mother and her daughter These clinical observations suggested that S L E may possibly be a familial disorder

In a study of two pedigrees, Larsson and Leonhardt [4] found higher mean serum-γ-globulin levels in siblings of patients with S L E and their children than in controls living under the same environmental conditions The siblings had higher mean γ-globulin values than the first cousins, and the siblings' children than the second cousins Larsson and Leonhardt considered that familial hypergammaglobulinæmia and familial S L E were possibly closely related and were *manifestations of* an underlying, genetically determined tendency to overproduction of γ-globulin Holman and Deicher [8] found " distinct hypergammaglobulinæmia " in 11 of 57 relatives from 18 families of patients with S L E , and Rodnan et al [9] found *definite* hypergammaglobulinæmia in 12 of 59 relatives, thus confirming the observations of Larsson and Leonhardt



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9 Rodnan G P, Maclachlan M J, Creighton A S *Clin Res* 1960, 8 197

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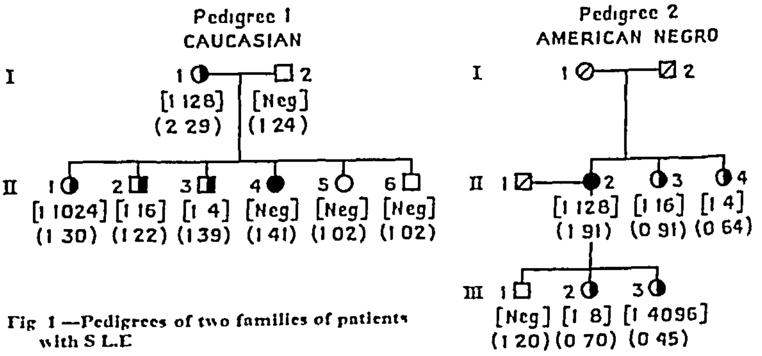

Fig 1 —Pedigrees of two families of patients with S L.E

● S L E

◐ —positive test for antinuclear factors

○ —negative test for antinuclear factors

⊘ —not tested

[ ] —titre of antinuclear factors

( ) —serum γ globulin (g per 100 ml)

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9 Rodnan G P Maclachlan M J, Creighton, A S *Clin Res* 1960, 8, 197

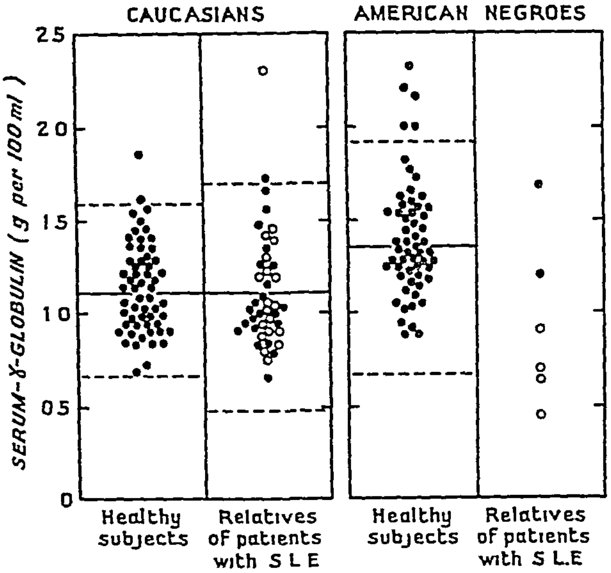

Fig 2.—Serum-γ-globulin levels in healthy subjects and in relatives of patients with S.L.E.

The mean values are given by continuous lines and two standard deviations by interrupted lines

○ = patients with positive tests for antinuclear factors
● = patients with negative tests for antinuclear factors

We found few relatives with hypergammaglobulinæmia, but somewhat high γ-globulin levels were found in 5 of 7 members of pedigree 1 Unusually low γ-globulin levels were found in 4 of 5 members of pedigree 2 This finding is of interest in view of the reported development of an arthritis resembling rheumatoid arthritis in almost half of 16 children with the congenital form of agammaglobulinæmia, and of collagen disease in patients with congenital and acquired agammaglobulinæmia [10]

The most striking abnormality found was the high prevalence of positive tests for antinuclear factors in the serum of relatives of patients with S.L E The results strongly suggest that an abnormal protein or proteins with an affinity for cell nuclei in vitro are present in the serum of about half the relatives By contrast, positive tests for antinuclear factors were found in the serum of only 1 of 50 subjects with diseases unrelated to S L E and in none of the 40 healthy subjects studied Hargraves' cells have been reported in about 12% of patients with rheumatoid arthritis [11] and occasionally in other so-called collagen diseases We found positive tests for antinuclear factors in the serum of only 5 of 35 patients with these disorders Thus the prevalence of positive tests for antinuclear factors was considerably higher in relatives of patients with S L E than in patients with rheumatoid arthritis, scleroderma, and dermatomyositis As rheumatoid arthritis and positive serological tests for rheumatoid factor appear to be commoner in relatives of patients with S L E that in the general population,[8] [9] relatives of patients with S L E may possibly comprise at least a proportion of the patients with clinical rheumatoid arthritis and positive Hargraves' cells or antinuclear factors

The ætiology of systemic lupus erythematosus is still unknown In recent years abundant evidence has been accumulated that the serum of patients with S L E contains several abnormal γ-globulins These abnormal γ-globulins, which react with cells or cell constituents in vitro, can probably be classified as auto-immune antibodies Patients with S L E also show increased responsiveness to foreign antigens [12] The mechanism underlying the appearance of autoimmune antibodies and the increased sensitivity to foreign antigens is still poorly understood Both these abnormalities, however, point to a derangement in the system regulating "immunological homœstasis" The data reported here indicate that this derangement probably has an hereditary basis, and suggest that overt disease may result from exposure to various antigens and other provocative stimuli in persons with the appropriate hereditary abnormality in the homœstasis of the antibody-producing system

We wish to thank Mrs Anne Doig, Mrs Janet Rezaian, and Mr Marcellus Moore for technical assistance This study was supported in part by a grant (H2253) from the United States Public Health Service, National Institutes of Health, Bethesda, Maryland

VICTOR E POLLAK *
M B W srand, M.R C P.E
ENNO MANDEMA †
M.D Groningen
ROBERT M KARK
F R C P, F A C P

Departments of Medicine,
Presbyterian-St Luke s Hospital,
Cook County Hospital,
Research and Educational Hospitals,
University of Illinois College of Medicine,
Chicago, Illinois, U S.A

BLOOD-GROUP DISTRIBUTION IN MEGALOBLASTIC ANÆMIA OF PREGNANCY

FOLIC-ACID deficiency in pregnancy is characterised by the appearance of megaloblasts in the marrow In the most severe cases these are of the classical Ehrlich type, as seen in addisonian anæmia, whereas transitional megaloblasts are encountered in the milder forms of the disease More recent studies have shown that folic-acid depletion frequently occurs in late pregnancy without producing megaloblastic changes in the marrow,[13] although the hæmoglobin-level can generally be raised by the administration of folic acid [14]

Folic-acid deficiency in pregnancy can thus be conveniently classified in four categories

Grade 0—The marrow remains entirely normoblastic and folic-acid depletion can be diagnosed with certainty only by folic-acid assays In these cases the hæmoglobin level can usually be raised by folic-acid therapy

Grade 1—The mildest form of megaloblastic anæmia, in which the marrow is predominantly normoblastic, though it contains a number of transitional megaloblasts Diagnosis in such cases may need confirmation by other criteria—e g, a raised serum-iron level and satisfactory response to folic-acid therapy

Grade 2—The marrow is predominantly megaloblastic, but the majority of cells is of the transitional type.

Grade 3—A florid megaloblastic marrow in which the classical Ehrlich type of megaloblast predominates The marrow picture in these cases is indistinguishable from that seen in addisonian anæmia

Obviously, the marrow-changes in these four categories reflect, to some extent, the degree of folic-acid depletion in any given person It would be an oversimplification to assume from this that all pregnant women with folic-acid

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[10] Gitlin D, Gross P A M Janeway C A. *New Engl J Med* 1960, 260 72

[11] Friedman I A, Sickley J E, Poske, R M, Black A Bronsky D Hartz, W H Jr Feldhake, C Reeder, P S Katz, E M. *Ann intern Med* 1957, 46 1113

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[12] Holman H R. *Ann Rev Med* 1960 11 231

[13] Chanarin, I MacGibbon B M. O Sullivan W J, Mollin D L *Lancet* 1959, ii 634

[14] Giles C, Burton, H *Brit med J* 1960 ii 636

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Undiluted	33	40	3	20
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51 patients with S L E were studied When the first serum drawn from each of these patients was examined, specific nuclear fluorescence was found with serum diluted 1 4 or higher in 45 In all, 151 specimens of serum from these 51 patients have been examined to date, *and specific nuclear fluorescence with serum diluted 1 4* or higher was observed with 131 specimens As antinuclear factors were found when the serum was diluted 1 4 in only 1 of 90 sera examined as controls, the demonstration of antinuclear factors in serum diluted 1 4 or more appeared to distinguish patients with S L E from healthy subjects and those with a variety of other diseases The test was therefore called positive when antinuclear factors were demonstrated in serum diluted 1 4 or more

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Relationship	Female relatives		Male relatives	
	Positive tests	Negative tests	Positive tests	Negative tests
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Siblings	6	4	4	5
Offspring	2	0	2	3
Maternal siblings	3	1	1	1
First cousins	1	0	0	1
Grandparents	0	3	0	3
Totals	17	9	7	17

Single serum samples from 50 members of families of 12 patients with S L E were studied (tables I and II) Specific nuclear fluorescence was demonstrated with serum diluted 1 4 or more in 24 instances *Positive tests* were found with the sera of 19 of 36 first-degree relatives tested, and with the sera of 5 of 14 second-degree relatives Positive tests were found in 17 of 26 female relatives but in only 7 of 24 male relatives The difference in the frequency of positive tests in male and female relatives is significant (χ^2=5 2, P= <0 05), but further observations on this sex difference are necessary

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In the second pedigree the propositus (II 2) was a 21-year-old American Negro housewife with typical S L E Positive tests for antinuclear factors were found in the serum of the patient, her 2 younger sisters, her 5-year-old son, and 3-year-old daughter (III 3)—in whom the titre of antinuclear factors was 1 4096

The serum-γ-globulin levels were estimated by the Biuret reagent and filterpaper electrophoresis They are compared in fig 2 with values from 62 healthy Caucasian (1 13±0 23 g per 100 ml) and 62 healthy American Negro subjects (1 37±0 30 g per 100 ml) Elevated γ-globulin levels (>2 S D above the mean of the controls) were found in only 3 Caucasian relatives and 2 Caucasian controls Decreased γ-globulin levels (>2 S D below the mean of the controls) were found in 1 Caucasian and 2 Negro relatives 5 of the 6 Negro relatives were members of one family (pedigree 2) The difference between the γ-globulin levels in the members of this family and those in the controls was significant (χ^2=17 2, P= <0 01)

DISCUSSION

In 1957 Leonhardt [2] reported S L E in 3 of 14 siblings He pointed out that at that time there were only four reported instances of the familial occurrence of S L E

Subsequently, Agranat et al [3] Larsson and Leonhardt,[4] and Lawrence [5] have each reported S L E in 2 sisters Wagenhals and Burgeson [6] observed the disease in twin sisters Griffin et al [7] found S L E in a father and his daughter, and Holman and Deicher [8] reported its occurrence in a mother and her daughter These clinical observations suggested that S L E may possibly be a familial disorder

In a study of two pedigrees, Larsson and Leonhardt [4] found higher mean serum-γ-globulin levels in siblings of patients with S L E and their children than in controls living under the same environmental conditions The siblings had higher mean γ-globulin values than the first cousins, and the siblings' children than the second cousins Larsson and Leonhardt considered that familial hypergammaglobulinæmia and familial S L E were possibly closely related and were manifestations of an underlying, genetically determined tendency to over-production of γ-globulin Holman and Deicher [8] found " distinct hypergammaglobulinæmia " in 11 of 57 relatives from 18 families of patients with S L E, and Rodnan et al [9] found definite hypergammaglobulinæmia in 12 of 59 relatives, thus confirming the observations of Larsson and Leonhardt

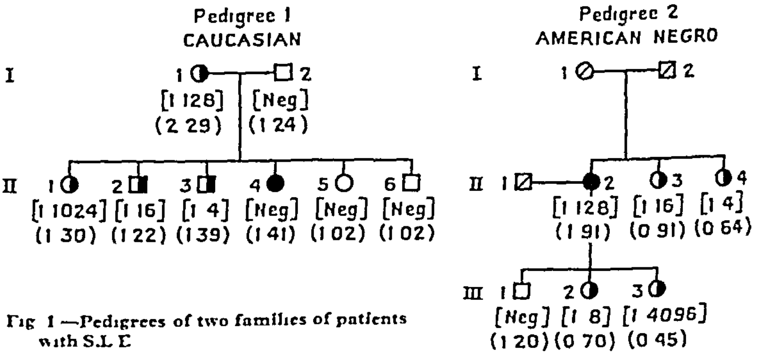

Fig 1 —Pedigrees of two families of patients with S.L E

● =S L E
◐ —positive test for antinuclear factors
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9 Rodnan, G P , Maclachlan M J , Creighton A S *Clin Res* 1960 8, 197

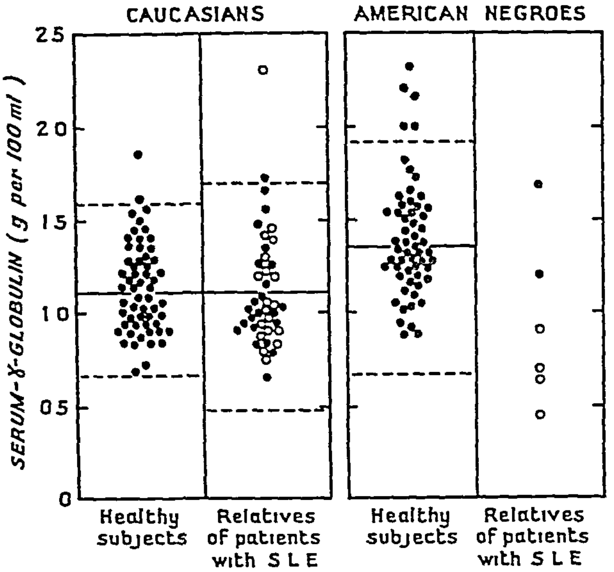

Fig 2.—Serum-γ-globulin levels in healthy subjects and in relatives of patients with S.L.E.

The mean values are given by continuous lines and two standard deviations by interrupted lines.

○ = patients with positive tests for antinuclear factors
● = patients with negative tests for antinuclear factors

We found few relatives with hypergammaglobulinæmia, but somewhat high γ-globulin levels were found in 5 of 7 members of pedigree 1. Unusually low γ-globulin levels were found in 4 of 5 members of pedigree 2. This finding is of interest in view of the reported development of an arthritis resembling rheumatoid arthritis in almost half of 16 children with the congenital form of agammaglobulinæmia, and of collagen disease in patients with congenital and acquired agammaglobulinæmia.[10]

The most striking abnormality found was the high prevalence of positive tests for antinuclear factors in the serum of relatives of patients with S.L.E. The results strongly suggest that an abnormal protein or proteins with an affinity for cell nuclei in vitro are present in the serum of about half the relatives. By contrast, positive tests for antinuclear factors were found in the serum of only 1 of 50 subjects with diseases unrelated to S.L.E. and in none of the 40 healthy subjects studied. Hargraves' cells have been reported in about 12% of patients with rheumatoid arthritis[11] and occasionally in other so-called collagen diseases. We found positive tests for antinuclear factors in the serum of only 5 of 35 patients with these disorders. Thus the prevalence of positive tests for antinuclear factors was considerably higher in relatives of patients with S.L.E. than in patients with rheumatoid arthritis, scleroderma, and dermatomyositis. As rheumatoid arthritis and positive serological tests for rheumatoid factor appear to be commoner in relatives of patients with S.L.E. that in the general population,[8] [9] relatives of patients with S.L.E. may possibly comprise at least a proportion of the patients with clinical rheumatoid arthritis and positive Hargraves' cells or antinuclear factors.

The ætiology of systemic lupus erythematosus is still unknown. In recent years abundant evidence has been accumulated that the serum of patients with S.L.E. contains several abnormal γ-globulins. These abnormal γ-globulins, which react with cells or cell constituents in vitro, can probably be classified as auto-immune antibodies. Patients with S.L.E. also show increased responsiveness to foreign antigens.[12] The mechanism underlying the appearance of autoimmune antibodies and the increased sensitivity to foreign antigens is still poorly understood. Both these abnormalities, however, point to a derangement in the system regulating "immunological homœstasis." The data reported here indicate that this derangement probably has an hereditary basis, and suggest that overt disease may result from exposure to various antigens and other provocative stimuli in persons with the appropriate hereditary abnormality in the homœstasis of the antibody-producing system.

We wish to thank Mrs Anne Doig, Mrs Janet Rezaian, and Mr Marcellus Moore for technical assistance. This study was supported in part by a grant (H2253) from the United States Public Health Service, National Institutes of Health, Bethesda, Maryland.

Department of Medicine,
Presbyterian-St Luke's Hospital,
Cook County Hospital
Research and Educational Hospitals,
University of Illinois College of Medicine,
Chicago, Illinois, U.S.A.

VICTOR E POLLAK*
M B W'srand, M.R C.P.E

ENNO MANDEMA†
M.D Groningen

ROBERT M KARK
F R C P, F A C P

BLOOD-GROUP DISTRIBUTION IN MEGALOBLASTIC ANÆMIA OF PREGNANCY

FOLIC-ACID deficiency in pregnancy is characterised by the appearance of megaloblasts in the marrow. In the most severe cases these are of the classical Ehrlich type, as seen in addisonian anæmia, whereas transitional megaloblasts are encountered in the milder forms of the disease. More recent studies have shown that folic-acid depletion frequently occurs in late pregnancy without producing megaloblastic changes in the marrow,[13] although the hæmoglobin-level can generally be raised by the administration of folic acid.[14]

Folic-acid deficiency in pregnancy can thus be conveniently classified in four categories:

Grade 0.—The marrow remains entirely normoblastic and folic-acid depletion can be diagnosed with certainty only by folic-acid assays. In these cases the hæmoglobin level can usually be raised by folic-acid therapy.

Grade 1.—The mildest form of megaloblastic anæmia, in which the marrow is predominantly normoblastic, though it contains a number of transitional megaloblasts. Diagnosis in such cases may need confirmation by other criteria—e.g., a raised serum-iron level and satisfactory response to folic-acid therapy.

Grade 2.—The marrow is predominantly megaloblastic, but the majority of cells is of the transitional type.

Grade 3.—A florid megaloblastic marrow in which the classical Ehrlich type of megaloblast predominates. The marrow picture in these cases is indistinguishable from that seen in addisonian anæmia.

Obviously, the marrow-changes in these four categories reflect, to some extent, the degree of folic-acid depletion in any given person. It would be an oversimplification to assume from this that all pregnant women with folic-acid

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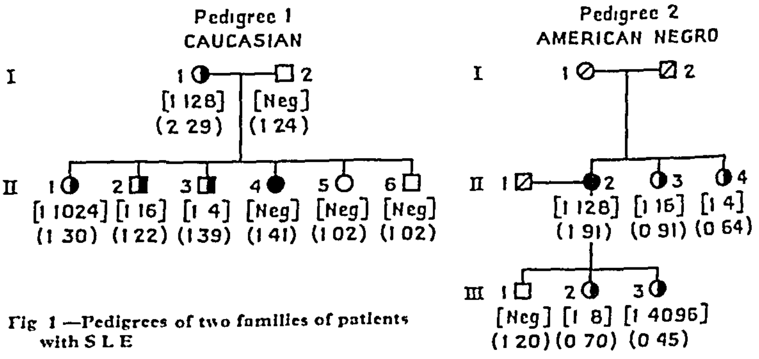

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Cooling and rewarming is by means of a heat-exchanger constructed from stainless steel A filter and bubble trap are incorporated in the arterial outflow line Two sucker lines are provided which deliver their blood on to five perforated plates lightly coated with anti-foam The output of the arterial pump and of the pump controlling the suction lines can be varied by two simple hand controls The apparatus and tubing in contact with blood is sterilised in ethylene oxide for 24 hours before use

The hypothermic and heating equipment is contained within a low trolley which acts as a mount for the heart-lung machine In this way the apparatus, while remaining compact, is entirely self-contained The cold source is supplied with a mixture of ice and water kept in a lagged 2 gal tank, and hot water is kept thermostatically controlled at about 40°C in a separate tank

Application

The apparatus has been used in twenty-five dog experiments In addition, four children have been operated on, with one death In use the machine requires very little adjustment, the running being in the hands of one technician

The apparatus has been constructed for me by Mr A F Turner in the Guy s Hospital Medical School workshop, and it will be available through Cardiac Recorders, Ltd, Weymouth Street, London, W 1

Guy s Hospital
London S E 1

D N Ross
M B, B SC Cape Town, F R C S

Reviews of Books

Medical and Dental Aspects of Fluoridation

W A Cannell, M R C S, D P H, L D S London Lewis 1960 Pp 125 15*s*

Most of the growing literature of fluoridation and fluorine is scattered in various journals A great deal of the research has been done in the United States, and the few books that have appeared since Roholm's classic text in 1937 have been published there A British survey of the present state of knowledge is welcome, and Dr Cannell gives a concise and readable summary, with an account of some important original work on the effect of trace elements

It is a relief to find a book that deliberately does not discuss the various fluoridation trials in the United States So much has been written about them and their real and alleged shortcomings that there is a risk of losing sight of one of the fundamental issues—the physiological and biochemical effects of fluorides Too little is generally known about the systemic effects of fluorides, and Dr Cannell's book should go a long way towards dispelling this ignorance, especially among the opponents of fluoridation

The chapters on the pharmacology of the fluorides and on the calcification of skeletal and dental tissues are particularly good Speculation is kept to a minimum, and the facts are presented fairly, and without bias Not everyone will agree with Dr Cannell in his excursion into the field of logical causality (p 69), but the inescapability of fluorides renders his argument an attractive one

The final chapter, on the public-health aspects, puts forward a well-reasoned case for the fluoridation of water-supplies Other possible means of administration are discussed in the light of recent research The bibliography is comprehensive and up to date, though there is no reference to Mackenzie's extensive review[1]

This is probably one of the best accounts of fluorides and their effects that has been published for some time

Pathology of Infancy and Childhood

Agnes R Macgregor, M D, F R C P E, F R C O G, reader in pathology, Edinburgh University Edinburgh and London E & S Livingstone 1960 Pp 631 75*s*

A volume concerned entirely with pædiatric pathology has been urgently needed by many pathologists, and the gap has been partly filled by this book in which Dr Macgregor incorporates the experience of her many years as an authority on this subject It is a simple book it makes no pretension to being a work of reference for pædiatric pathologists, but has been designed for the pathologist whose main work and interests are with older patients Most conditions which he is likely to meet are considered adequately, with proper regard for their relative importance and incidence Bearing in mind that the great majority of necropsies are on infants dying in the perinatal period, notes on necropsy technique and detailed practical accounts of perinatal conditions are included Many facts in this part of the book rarely appear in print and are usually appreciated only after considerable experience The section dealing with developmental anomalies could have been fortified by the inclusion of notes on embryology, supported by diagrams Since many hospitals have cardiothoracic units, and deaths from cardiovascular anomalies often form a big part of pædiatric necropsy work, the account of these anomalies may be too superficial Although the photographs of specimens of malformed hearts are generally self-explanatory, a few diagrams would have enhanced clarity A lack of uniformity between different sections of the book is mainly due to the omission of conditions which are not peculiar to infants or children, or which are well described in standard textbooks of pathology But a few relatively important diseases are treated rather briefly, and many less common conditions are not mentioned even by reference to the literature Although the references are well chosen and up to date, the bibliography will be little help to the pathologist faced with an unusual case

This book will be particularly useful to those embarking upon a career in pathology or pædiatrics Its value to the established pathologist is limited, but it will be enjoyed by those who appreciate the signs of the author's wide experience

The Chemical Senses in Health and Disease

H Kalmus, SC D, M D, reader in biology, University of London, S J Hubbard, B SC, PH D, lecturer in physiology, University College, London Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1960 Pp 95 30*s*

No disciple of Brillat-Savarin needs to be reminded of the importance of the chemical senses—concerned as they are with taste and smell But many may be surprised at the complexity of the physiological processes subserving the art of transcendental gastronomy Who would have suspected, for instance, that over 60 volatile substances contribute to the aroma of coffee? This suggests almost endless permutation of naturally occurring odours and many kinds of odour-receptors On the other hand, only four basic tastes—sour, salt, sweet, and bitter—are firmly established The interplay of taste and smell, the importance of these chemical senses in behaviour both in animals and man, some curious and interesting genetical variations in both senses, and lines of future research and their practical importance are all discussed in this book The psychological aspects—in some ways the most fascinating of any—are also briefly mentioned The book is short and well worth the attention of physiologist and clinician It is a pity the price is so high

The Early History of Surgery

W J Bishop, editor, *Medical History* London Robert Hale 1960 Pp 192 18*s*

At a time when road travel is becoming increasingly dangerous, it is good to discover that some at least of its former hazards have been mitigated Richard Wiseman, writing in 1676, described the misadventure which befell " a gentleman of about thirty years of age, who was coming out of Hertfordshire through Tottenham and riding upon the causeway near an inn when, one emptying a chamber pot out of the window deficiency are equally liable to develop advanced megaloblastic anæmia. A study of the blood-group distribution of patients with megaloblastic anæmia of pregnancy has shown that cases with a grade-3 type of marrow, in which the classical Ehrlich type of megaloblasts are encountered, probably represent a special group which appears to be genetically determined.

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[1] Mackenzie E F W *Lancet*, 1952 i 961

The blood-group distribution of 175 patients with megaloblastic anæmia of pregnancy was compared with that of 3500 routine antenatal cases in the same district*. As seen in table I, the only deviation from the norm is an increase in the incidence of blood-group A in patients with megaloblastic anæmia, but this is less than the group A preponderance reported in addisonian anæmia.[15]

TABLE I—BLOOD-GROUP DISTRIBUTION IN MEGALOBLASTIC ANÆMIA OF PREGNANCY*

Blood group	Routine antenatal (3500 cases)	Megaloblastic anæmia of pregnancy			
		All grades (175 cases)	grade 3 (77 cases)	grade 2 (59 cases)	grade 1 (39 cases)
O	46%	43%	34%	48%	56%
A	42%	50%	60%	46%	36%
B	9%	5%	5%	3%	5%
AB	3%	2%	1%	3%	3%

When, however, cases of megaloblastic anæmia of pregnancy were classified according to their hæmatological grade (from 1 to 3), and the blood-group distribution calculated separately for each grade, it became obvious that there was only one category with a definite group-A preponderance—namely, grade 3—composed of those cases in which the marrow most closely resembles that of addisonian anæmia. Table I shows that the incidence of blood-group A in 77 cases in category 3 is 60%, compared with a proportion of 42% in the controls. As seen in table II, this difference is statistically significant ($P < 0.01$). On the other hand, the group-A incidence in those patients who were classified in grades 1 and 2 is 42%, which closely approaches the normal distribution.

TABLE II—INCIDENCE OF GROUP-A IN MEGALOBLASTIC ANÆMIA OF PREGNANCY

Megaloblastic anæmia of pregnancy	Number of cases	Group A incidence	χ^2	P
All grades	175	50%	4.18	<0.05
Grade 3	77	60%	9.16	<0.01
Grade 2	59	46%	0.30	>0.5
Grade 1	39	36%	0.43	>0.5
Grades 1 and 2	98	42%	0.04	>0.5
Controls	3500	42%		

Analysis of clinical and hæmatological findings in women with the various grades of megaloblastic anæmia shows that grade-3 cases tend to present with more severe anæmia, higher serum-iron levels, and usually show a greater reticulocyte response to folic-acid therapy. In other respects, patients in the various categories do not appear to differ. Their age-distribution is similar and the incidence of achlorhydria is approximately the same. A history of an inadequate diet in pregnancy appears with equal frequency in all categories, and the previous administration of iron does not seem to affect the marrow-picture. Gastrointestinal symptoms, especially anorexia and ulceration of the mouth, occur equally often with lesser degrees of megaloblastosis.

It would obviously be premature to draw definite conclusions from the blood-group distribution in a single series of cases from one district. These findings suggest, however, that while folic-acid deficiency, with or without megaloblastic changes in the marrow, is a frequent occurrence in late pregnancy, patients with advanced megaloblastic anæmia constitute a special group in which there is an inherited predisposition to the disease. The report by Giles and Burton[14] of 13 out of 41 cases of megaloblastic anæmia of pregnancy, with evidence of diminished fat absorption, has already pointed to a constitutional factor in the ætiology of the disease. It is perhaps significant that a grade-3 type of marrow was found in 10 of these 13 cases.

My thanks are due to Mr. A. H. Iliffe, of the University College of North Staffordshire, for the statistical analysis, to Dr. R. B. McConnell for his helpful advice, to Dr. A. J. McCall for his help and encouragement, and to the research fund of the Birmingham Regional Hospital Board for its assistance.

City General Hospital,
Stoke-on-Trent

C. GILES
M.D., B.SC. Manc.

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[15] Fraser Roberts, J. A. *Brit. med. Bull.* 1959, 15, 129.

New Inventions

A HEART-LUNG MACHINE FOR INFANTS AND YOUNG CHILDREN

MOST heart-lung machines are designed for patients of 3 to 5 years and over. Moreover, particular attention has been directed towards apparatus capable of maintaining the circulation in full-sized adults. A number of congenital defects are responsible for death within the first year of life[1], but existing machines, with their relatively large priming volume, are not readily adaptable to the low flows and blood-volumes in this age-group.

The following heart-lung circuit has been designed to provide flows up to 1.2 litres per min., with a priming volume of 500–750 ml.

Apparatus

Basically this is a scaled-down version of the model in current clinical use.[2] The oxygenator is of the rotating disc variety, and a heat-exchanger is included in the circuit. The apparatus is entirely self-contained, being provided with its own source of heating and cooling fluids (see figure).

Two complete oxygenators are available (22 and 34 cm. long). The smaller provides for flows up to 700 ml. per min., and the larger for flows up to 1200 ml. per min. The discs are of stainless steel, 7.8 cm. in diameter and spaced 4 mm. apart. Spacing of the discs at less than 4 mm. causes foaming. No silicone or anti-foam is required in the oxygenator. The rotation speed of the discs is 120 r.p.m.

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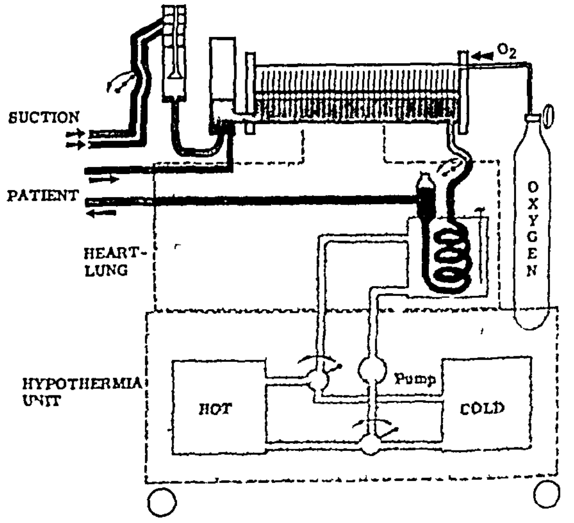
1. Bonham Carter, R. E., Waterston, D. J. *Brit. Heart J.* 1957, 19, 589.
2. Ross, D. N. *Brit. med. J.* 1960, ii, 571.



Circuit diagram of the complete apparatus showing the hypothermia unit below.

Cooling and rewarming is by means of a heat-exchanger constructed from stainless steel. A filter and bubble trap are incorporated in the arterial outflow line. Two sucker lines are provided which deliver their blood on to five perforated plates lightly coated with anti-foam. The output of the arterial pump and of the pump controlling the suction lines can be varied by two simple hand controls. The apparatus and tubing in contact with blood is sterilised in ethylene oxide for 24 hours before use.

The hypothermic and heating equipment is contained within a low trolley which acts as a mount for the heart-lung machine. In this way the apparatus, while remaining compact, is entirely self-contained. The cold source is supplied with a mixture of ice and water kept in a lagged 2 gal. tank, and hot water is kept thermostatically controlled at about 40°C in a separate tank.

Application

The apparatus has been used in twenty-five dog experiments. In addition, four children have been operated on, with one death. In use the machine requires very little adjustment, the running being in the hands of one technician.

The apparatus has been constructed for me by Mr. A. F. Turner in the Guy's Hospital Medical School workshop, and it will be available through Cardiac Recorders, Ltd., Weymouth Street, London, W.1.

Guy's Hospital,
London, S.E.1

D. N. ROSS
M.B., B.SC. Cape Town, F.R.C.S.

Reviews of Books

Medical and Dental Aspects of Fluoridation

W. A. CANNELL, M.R.C.S., D.P.H., L.D.S. London: Lewis. 1960. Pp. 125. 15s.

MOST of the growing literature of fluoridation and fluorine is scattered in various journals. A great deal of the research has been done in the United States, and the few books that have appeared since Roholm's classic text in 1937 have been published there. A British survey of the present state of knowledge is welcome, and Dr. Cannell gives a concise and readable summary, with an account of some important original work on the effect of trace elements.

It is a relief to find a book that deliberately does not discuss the various fluoridation trials in the United States. So much has been written about them and their real and alleged shortcomings that there is a risk of losing sight of one of the fundamental issues—the physiological and biochemical effects of fluorides. Too little is generally known about the systemic effects of fluorides, and Dr. Cannell's book should go a long way towards dispelling this ignorance, especially among the opponents of fluoridation.

The chapters on the pharmacology of the fluorides and on the calcification of skeletal and dental tissues are particularly good. Speculation is kept to a minimum, and the facts are presented fairly, and without bias. Not everyone will agree with Dr. Cannell in his excursion into the field of logical causality (p. 69), but the inescapability of fluorides renders his argument an attractive one.

The final chapter, on the public-health aspects, puts forward a well-reasoned case for the fluoridation of water-supplies. Other possible means of administration are discussed in the light of recent research. The bibliography is comprehensive and up to date, though there is no reference to Mackenzie's extensive review.[1]

This is probably one of the best accounts of fluorides and their effects that has been published for some time.

Pathology of Infancy and Childhood

AGNES R. MACGREGOR, M.D., F.R.C.P.E., F.R.C.O.G., reader in pathology, Edinburgh University. Edinburgh and London: E. & S. Livingstone. 1960. Pp. 631. 75s.

A VOLUME concerned entirely with pædiatric pathology has been urgently needed by many pathologists, and the gap has been partly filled by this book in which Dr. Macgregor incorporates the experience of her many years as an authority on this subject. It is a simple book: it makes no pretension to being a work of reference for pædiatric pathologists, but has been designed for the pathologist whose main work and interests are with older patients. Most conditions which he is likely to meet are considered adequately, with proper regard for their relative importance and incidence. Bearing in mind that the great majority of necropsies are on infants dying in the perinatal period, notes on necropsy technique and detailed practical accounts of perinatal conditions are included. Many facts in this part of the book rarely appear in print and are usually appreciated only after considerable experience. The section dealing with developmental anomalies could have been fortified by the inclusion of notes on embryology, supported by diagrams. Since many hospitals have cardiothoracic units, and deaths from cardiovascular anomalies often form a big part of pædiatric necropsy work, the account of these anomalies may be too superficial. Although the photographs of specimens of malformed hearts are generally self-explanatory, a few diagrams would have enhanced clarity. A lack of uniformity between different sections of the book is mainly due to the omission of conditions which are not peculiar to infants or children, or which are well described in standard textbooks of pathology. But a few relatively important diseases are treated rather briefly, and many less common conditions are not mentioned even by reference to the literature. Although the references are well chosen and up to date, the bibliography will be little help to the pathologist faced with an unusual case.

This book will be particularly useful to those embarking upon a career in pathology or pædiatrics. Its value to the established pathologist is limited, but it will be enjoyed by those who appreciate the signs of the author's wide experience.

The Chemical Senses in Health and Disease

H. KALMUS, SC.D., M.D., reader in biology, University of London; S. J. HUBBARD, B.SC., PH.D., lecturer in physiology, University College, London. Springfield, Ill.: Charles C Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 95. 30s.

NO disciple of Brillat-Savarin needs to be reminded of the importance of the chemical senses—concerned as they are with taste and smell. But many may be surprised at the complexity of the physiological processes subserving the art of transcendental gastronomy. *Who would have suspected, for* instance, that over 60 volatile substances contribute to the aroma of coffee? This suggests almost endless permutation of naturally occurring odours and many kinds of odour-receptors. On the other hand, only four basic tastes—sour, salt, sweet, and bitter—are firmly established. The interplay of taste and smell, the importance of these chemical senses in behaviour both in animals and man, some curious and interesting genetical variations in both senses, and lines of future research and their practical importance are all discussed in this book. The psychological aspects—in some ways the most fascinating of any—are also briefly mentioned. The book is short and well worth the attention of physiologist and clinician. It is a pity the price is so high.

The Early History of Surgery

W. J. BISHOP, editor, *Medical History*. London: Robert Hale. 1960. Pp. 192. 18s.

AT a time when road travel is becoming increasingly dangerous, it is good to discover that some at least of its former hazards have been mitigated. Richard Wiseman, writing in 1676, described the misadventure which befell "a gentleman of about thirty years of age, who was coming out of Hertfordshire through Tottenham and riding upon the causeway near an inn when, one emptying a chamber pot out of the window

as he was passing by, his horse started and rushed violently between a signpost and a tree which supported part of the sign The poor gentleman was beaten off his horse and lay stunned upon the ground " This case, and Wiseman's successful management of it, is one of the many which Mr Bishop uses to illustrate the evolution of surgery His book is happily written in a style easily intelligible to the layman, yet technical enough to appeal to doctors as well, and, as might be expected from the author's status as an antiquarian, it is distinguished by a meticulous attention to accuracy Even in such a matter as the emergency operation on King Edward VII, it is noted that it was never officially stated whether or not an appendicectomy had been performed

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[1] Mackenzie, E. F. W. Lancet, 1952, i, 961.

The Healthy Child

His Physical, Psychological, and Social Development Editors HAROLD C STUART, M D, emeritus professor of maternal and child health, Harvard University School of Public Health, DANE G PRUGH, M D, associate professor of pædiatrics and psychiatry, University of Rochester School of Medicine and Dentistry Cambridge, Mass Harvard University Press London Oxford University Press 1960 Pp 507 80*s*

THIS book is written for all who work professionally with children, whether in the areas of medicine, education, social work, public health, nutrition, nursing, or psychology, and those who have contributed to it come from a correspondingly wide range of disciplines The emphasis is on " healthy development " and how it may best be protected or promoted The book presents in broad terms a picture of the child and his expected progress from conception to maturity It is concerned with him as an individual who is changing or developing according to natural laws and inborn potentialities It deals with the major aspects of his physical development and also with his psychosocial development and the factors which favour mental health Among its many interesting chapters is one on emotional changes in pregnancy Emphasising throughout the wide range of normal, the book is a valuable contribution to the increasing literature on the important subject of normality

Life's Long Journey

KENNETH WALKER, F R C S London Victor Gollancz 1960 Pp 191 21*s*

Mr Kenneth Walker writes, for the general public, to discount excessive claims for the material sciences in general, and in particular the supposition that natural selection sufficiently explains the course of human evolution and that scientific control could or should direct its future course, if any

In the earlier chapters he seems to postulate " life " as a forward-looking entity planning its own development, but throughout the book " Nature ", without inverted commas, appears as experimenter and giver or withholder of gifts, and it is not at all clear whom or what he regards as the " eternal mover ", though he makes a firm claim for the life spiritual and the reality of mystical experience

Like some others, Mr Walker regards the present population explosion as more dangerous to humanity than the atom bomb and fears our despairing recourse to Communist termitism He is surely unjust to Ecclesiastes (" cast thy bread upon the waters ") in ascribing to him and not to Proverbs the advice to look to the ant for exemplar, but that, in the present human predicament, the termitary is terrifying to contemplate is sure enough

No Crying in this Cradle

The Expectant and Nursing Mother's Bedside Book ELIZABETH G MORRISON, S R N, S C M, M T S, JOAN GOLDMAN London Ernest Benn 1960 Pp 159 15*s*

Elizabeth Morrison has had a vast experience of reading and answering letters from mothers because for thirty years she has run the correspondence columns in *Nursery World* But one wonders just how much practical experience she has had, and how recently Some of the advice she gives is outdated—e g, " it is advisable to go specially easy on meat in the last month or two of pregnancy " There seems little point in advising an expectant mother not to eat mixed grill and telling her that it won't make her or the baby " *feel too good* " The book says that eiderdowns for babies "ought to be forbidden by an Act of Parliament ", not because they may smother the baby, but because " *nothing more effective exists to make the baby sweat* " Most of the book is an invective in favour of breast-feeding But the reasons why babies should be breast-fed whenever possible are poorly argued and unconvincing It is true that some doctors do not know much about normal babies, but it is doubtful whether many are as woefully ignorant as this book suggests Doubtless dissatisfied patients write in sorrow and anger to the magazines, and Sister Morrison must receive many such letters But to describe the doctor and baby clinic as " statistics-ridden prophets " who " yell the roof off with their denunciations " seems to be going rather far

Nevertheless, the book contains a good deal of sensible, practical advice of the kind that is being given daily by good doctors and nurses up and down the country

Clinical Bacteriology (2nd ed London Edward Arnold 1960 Pp 309 30*s*)—The duties of the bacteriologist in a hospital are to isolate pathogenic bacteria, to decide from collateral evidence and probability that these have some connection with the patient's illness, and—a recent development—to give guidance on the treatment of the infection to those responsible for the patient The identity of the organism is not vastly important (except to the epidemiologist) but custom at least demands that this shall be reported as accurately as possible It is this academic pride in going beyond the bare diagnosis and treatment which distinguishes the medical bacteriologist from the technician When Dr Joan Stokes' book first appeared it was the best benchbook for the medical bacteriologist which had been published and it remains so today The academic background (for which she still apologises) converts what might have been a mere cookery book into a readable and reliable guide to work at the bench The changes in this second edition add some new methods and take account of some recent advances in knowledge, but as before it is clear that all the recommendations are made in the light of personal experience

Demonstrations of Physical Signs in Clinical Surgery (13th ed Bristol John Wright 1960 Pp 928 75*s*)—In 1927 medical illustration was just emerging from the era of line drawings Some textbooks contained a few photographs, but they were often reproduced in poorly contrasting shades of grey, and the technique of colour printing was in its infancy When, therefore, in that year, the first edition of this book appeared, with its clear and vivid illustrations, students were quick to appreciate the efforts that Mr Hamilton Bailey and his publishers had made on their behalf It comes as no surprise to learn that, of the English editions alone, 177,000 copies have now been sold The latest edition contains more than four times as many pages and illustrations as the first, and if this growth-rate is maintained the twenty-fifth edition may well include an illustration of the typical lesion the volume produces by resting on the reader's knees Many pictures have been furnished by distinguished clinicians, some of whom would no doubt acknowledge that they were helped to their first academic successes by the very work to which they have now contributed

Principles of Orthopædic Surgery (London J & A Churchill 1960 Pp 799 150*s*)—Dr Paul E Colonna earlier published a book based on his lectures and teaching-rounds at the University of Pennsylvania This volume is an expanded form (a notable difference is the increased space devoted to traumatic lesions) but has in common with the earlier one a style of writing and printing that makes for easy reading even over long periods A few of the radiographs are not adequately reproduced, but the work is one of the very few which can be freely quoted on either side of the Atlantic without modification and with equal authority

THE LANCET

LONDON 12 NOVEMBER 1960

Malaria Research

WHEN LAVERAN discovered the malaria parasite in 1880 he opened the flood gates to a torrent of research which, despite ebbs and flows, today runs as strongly as ever It seemed at various times that the problems of malaria had been finally solved at the end of the century when the mechanism of transmission through mosquitoes was worked out, the way seemed open (or so at least Ross thought) for the control and abolition of the disease, in the years between the wars, and later, a range of drugs was synthesised which seemed to offer the perfect therapy, then the researches on the exo-erythrocytic cycle from 1936 onwards had apparently filled the last gap in our knowledge of the life-cycle of the parasite, while the discovery of dicophane (D D T) and other residual insecticides was thought to have provided the final answer to the problem of mosquito eradication. And today, although we may feel that the end is in sight, this impression may be as false as any similar one expressed earlier in the century

The study of malaria involves so many disciplines that a special composite science—malariology—inevitably developed, with its own institutes, journals, techniques, jargon, and specially its cadre of international workers who have devoted their lives to this fascinating borderline of research The malariologist must be prepared to dabble in entomology and protozoology, in clinical medicine, in chemotherapy and biochemistry, in statistics and genetics, even in such uncongenial subjects as engineering, administration, and sociology An issue of the *Bulletin of the World Health Organisation* [1] illustrates something of this range. It includes a paper by Sir GORDON COVELL (who has been awarded the Walter Reed medal for services to tropical medicine) on the potential danger of apyrexial carriers of malaria in constituting an unobvious reservoir of infection during eradication campaigns, an account by A. S ALVING (Chicago) of a new method of administering primaquine (the drug which destroys the exo-erythrocytic stages of the malaria parasite and prevents relapses) by reducing the toxicity of this invaluable drug, a complete analysis by L T BRUCE-CHWATT and C GOCKEL, of W.H.O, of the results of precipitin tests (carried out by B WEITZ, of the Lister Institute) of the stomach contents of anopheline mosquitoes, which showed that 48 out of 51 species fed to a greater or lesser extent on human blood, and other papers dealing with the action of dicophane and other residual insecticides R C MUIRHEAD-THOMSON, and G SACCA and Y GUY show how mosquitoes alter their habits after long exposure to dicophane—the so-called "behaviouristic resistance" The Colonial Pesticides Research Unit at Arusha suggests that the addition of a resin (ceredor) to gamma benzene hexachloride has provided the ideal insecticide for malaria control

Current research in malariology is as eclectic as ever Fundamental studies on the life-cycle of the parasite have been facilitated by using chimpanzees instead of volunteers, and BRAY [2] in Liberia, after finding that the liver of this ape is as susceptible as that of man to *Plasmodium vivax, ovale,* and *falciparum,* successfully demonstrated for the first time the tissue stages of the quartan parasite (*P malariæ*) by this technique There has been much controversy over the nature of nuclear division in malaria parasites, but BANO [3] has clearly demonstrated that the first division of the nucleus of the oocyst is meiotic, and that subsequent ones are mitotic, with a characteristic number of chromosomes in each of the seven species of plasmodia she studied The protective action of sickle-cell hæmoglobin against *P falciparum* was demonstrated by ALLISON [4] and other workers in 1954 and later More recently GILLES et al [5] have suggested that the possession of another hereditary trait—glucose-6-phosphate-dehydrogenase deficiency in red blood-cells—also has an inhibitory effect on the parasite.

Research on resistance has made much progress in the past few years In Algiers, SERGENT and PONCET [6] studied the development of resistance against chloroquine by *P berghei* in rats and mice, and introduced the term "mithridatism" for this feature The work of BISHOP [7] at the Molteno Institute went deeper and indicates that the resistance may have a mutational origin and be concerned with the metabolism of *p*-aminobenzoic acid and folic acid The resistance of several species of mosquitoes to insecticides presents a baffling problem in the eradication programme, and the genetic nature of this phenomenon has been shown at the Ross Institute, where DAVIDSON and JACKSON [8] demonstrated that resistance was of two independent types—to dicophane and dieldrin respectively, arising from single genetic factors, recessive in the former and semidominant in the latter, and applying to species of anopheline mosquitoes from as far apart as Africa, Indonesia, Iraq, and Central America This work has been confirmed to some extent by the cytological studies of FRIZZI and others [9] in Pavia, they have described in great detail the chromosome pattern of several species of mosquitoes, including susceptible and resistant forms These profound laboratory investigations stemmed directly from observations made in the field in Sokotu, Northern Nigeria, where RAMAKRISHNAN and ELLIOTT[10] noticed the sudden resistance to dieldrin of *Anopheles gambiæ* This is a good example of "incidental research", which has been a feature of malariology throughout its history

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[1] *Bull. Wld Hlth Org* 1960 22, no 6

[2] Bray, R. S *Brit med. J* 1959 ii 679

[3] Bano L. *Parasitology* 1959 49 559

[4] Allison A. C. *Brit med. J* 1954 i, 290

[5] Gilles, H. M. Watson-Williams, J, Taylor B S *Nature, Lond.* 1960, 185, 257

[6] Sergent, E. Poncet A. *Arch Inst Pasteur Algérie* 1959 37, 227

[7] Bishop, A. *Biol Rev* 1959 34, 445

[8] Davidson G, Jackson C. E. *Nature Lond* (in the press)

[9] D'Alessandro G Frizzi G, Mariani, M. *Bull. Wld Hlth Org* 1957 16, 859

Animal malaria, which has excited interest from the earliest days, has attracted fresh attention through the discovery[11] in the U S A that a strain of monkey malaria, isolated in London, readily infects man The parasite was named after G BASTIANELLI, the last of the great band of Italian malariologists, who died last year at the age of 96 This organism was being studied in three laboratories in the U S A , and, in all three, accidental infections occurred through the bites of infected mosquitoes The disease proved to be mild, and clinically and parasitologically resembled benign tertian malaria Subsequently G R COATNEY, D E EYLES, M E GETZ, and H K BEYE transmitted the infection back to monkeys and to volunteers, both by mosquitoes and by inoculation of blood containing parasites It was at once realised that here at last was direct evidence that monkeys might act as a reservoir of malaria in Nature, and that this infection might constitute a zoonosis Previously it had been well established[12] that another monkey parasite—*P knowlesi*—could easily affect man in its blood form, but mosquito transmission of this parasite to man has not yet been achieved, other simian parasites, such as *P malariæ* of chimpanzees and *P hylobati* of gibbons, are also suspected but not proved to be zoonoses *P cynomolgi bastianellii* (as this latest parasite is called) originated from a crab-eating monkey (*Macaca irus*) captured in Pahang, and the next stage of the research will be to discover first how many (if any) of the local inhabitants of this forested region are infected with the parasite, and secondly how widely it is distributed in the East Indies, Thailand, and the Far East With such a monkey reservoir of malaria, eradication may be an even more difficult undertaking than it seems at present, but, until the situation has been investigated fully, the extent of the danger cannot be assessed It may even be found that the parasite does not exist in Nature, but was the result of one of the flagrantly unnatural processes to which the parent strain had been subjected it was originally contaminated in both sexual and asexual forms with *P knowlesi*[13], it was flown across the Atlantic in iced blood, and it was maintained in a variety of exotic mosquitoes very different from its original insect vector

If malaria is to be eradicated from the world, these and other problems will have to be solved Even then the subject of malariology will not be extinguished, because much remains unknown about the malaria of lizards and birds, rats and lemurs, and bats and antelopes, and, though their parasites do not appear to affect man, the zoologist will be impelled to investigate them further, with their attendant insect hosts

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[10] Elliott R Ramakrishnan S *Nature Lond* 1956 177 532

[11] Eyles D E Coatney G R Getz M E *Science* 1960 131 1812

[12] Ciuca M Editura *Acad Rep pop Romine* 1955

[13] Hawking F Mellanby H Terry R J, Webber, W A F *Trans R Soc trop Med Hyg* 1957, 51 397

The Mongol Chromosome and Some Others

THE spate of new observations on human chromosome anomalies continues, and it seems worth following our recent attempt to survey the X chromosome disorders[1] with a similar account of one of the autosomes

Anomalies of the "mongol" chromosome (no 21 on the Denver system[2]) have been most studied indeed, apart from the sex chromosomes, this is the only one that can yet be associated in any but the most tentative way with a definite clinical syndrome Classical mongolism has now been shown beyond dispute to be caused by an extra chromosome, no 21[3-5] "Caused by", we would repeat though we do not know how the effect is produced, the relation is too strong to shelter behind the circumlocutory hedging implicit in the words "associated with" The production of "trisomy" of this kind, with three apparently normal chromosomes instead of the normal pair, by the process of non-disjunction during formation of the gamete, the effect of age on the incidence of non-disjunction, and the consequent explanation of the influence of maternal age on the incidence of mongolism are now familiar themes Interest is concentrating on certain cases in which the effect of trisomy-21 is produced by something other than the usual mechanism Such cases have been sought where youth of the mother, or (more certainly) evidence of familial transmission, has suggested that the ordinary non-disjunction mechanism has not been at work The first of these was reported by POLANI et al[6] earlier this year A mongol girl, one of a number examined because their mothers were much younger than usual at the time of their birth, was found to have the normal total number of 46 chromosomes One chromosome of the very characteristic medium-sized acrocentric group (nos 13–15, the "wishbones") was missing, and instead there was an atypical larger chromosome Ingeniously and most plausibly, POLANI et al accounted for this by assuming that the patient had a third no 21 present (thus accounting for her mongolism) but that this had fused with the missing no 14 (or thereabouts) to give the abnormal larger chromosome ("Fusion" oversimplifies the process, which is probably one of translocation, with exchange of material between two chromosomes if in this process a large fragment of one chromosome is exchanged for a small fragment of another, the result will be a large chromosome carrying most of the material of both and a small one carrying much less When these are separated in the process of gamete formation, imbalance will clearly result)

More recently PENROSE et al[7] have reported further "translocation" mongols One was much like the first, except that the extra no 21 was apparently joined to no 22 instead of no 14 In addition, they reported a most remarkable family. Two mongol sibs each had 46 chromosomes, with the same 21/15 translocation-fusion to account for it. In addition, three normal female relatives were found to have 45 chromosomes only. In them an essentially normal chromosome complement had apparently been affected by the "fusion" of one chromosome each from the pairs 15 and 21. In this family the translocation had obviously occurred at least in the great-grandparents. The mere joining together of two chromosomes had no recognisable effect, but the tendency to imbalance during gamete formation inseparable from this fusion gave rise to some offspring with too much chromosomal material, who were the mongols. The importance of this form of transmission has been established by the description of a very similar but even larger family group by CARTER et al.[8] The mechanism is fairly easy to follow from the diagram (fig. 4) of POLANI et al.[6]

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[1] *Lancet*, July 23 1960 p 191

[2] *ibid* 1960, i, 1063

[3] Lejeune J , Gautier, M , Turpin, R *C R Acad Sci , Paris* 1959, 248 602

[4] Jacobs P A Baikie A G , Court Brown, W M , Strong J A *Lancet*, 1959, i 710

[5] Böök, J A , Fraccaro, M Lindsten, J *Acta pædiat , Stockh* , 1959, 48 453

[6] Polani, P E Briggs J H Ford C E , Clarke C M , Berg J M *Lancet*, 1960, i, 721

[7] Penrose L S , Ellis, J R , Delhanty, J D A *ibid* Aug 20, 1960 p 409

Another remarkable family was reported by FRACCARO et al.[9] Here the mongol patient had 46 chromosomes, and an abnormality of the smaller chromosomes which was thought at first to represent the ordinary mongol trisomy of no. 21, with translocatory pseudo-fusion of two of the three to produce an abnormal single larger chromosome. His father, who appeared perfectly normal and is a minister of religion (and who may thus be the first exception to the rule that chromosomal anomalies and university degrees are incompatible) was found to have 47 chromosomes and to be trisomic for no. 19. The findings in this family admit of no simple explanation with our present knowledge, unless indeed (as seems unlikely) the diagnosis of the child as a mongol is at fault. But clearly we must expect some strange findings from the systematic examination of familial mongols. There are rumours of yet other variants on the way.

Anomalies of other chromosomes form a much more confusing picture. Trisomies of no. 17[10] and of one of the 13–15 group[11] seem well established. Trisomy of no. 22 is also not unlikely,[12] though identification of the chromosome present is not very certain (might it even have been an extra Y?) and its relation to the Sturge-Weber syndrome present cannot yet be accepted confidently. Trisomy of no. 11[13] and of no. 6[14] have both been claimed, but both cases had the double sex chromatin characteristic of the XXX syndrome,[15–17] and, as we[1] and others[18] have already suggested for the first of these, these may well both be examples of the XXX syndrome with perhaps minor irregularities of one of the X chromosomes concerned. Multiple trisomies have also been reported,[19][20] the most striking being FRACCARO et al.'s case[21] with 49 chromosomes altogether (nos. 8 and 11 trisomic, plus XXY), and indeed, except for the viability of the patients, there is nothing incredible about this, for the conditions which cause non-disjunction of one chromosome pair could quite reasonably be supposed equally to affect others. Perhaps the most nearly incredible of all the findings is the demonstration by BÖÖK and SANTESSON[22] of trisomy of every chromosome pair, giving a triploid individual with 69 chromosomes.

It is too early to hope to decipher the pattern which must lie behind the varied clinical manifestations of these anomalies. The sex-chromosome disorders present at least some trace of logic, and mongolism, though we have no glimmer of hint as to the mechanism by which the chromosome defect produces its highly specific effects, presents at least a consistent pattern. Of the others hardly any two cases are sufficiently alike for conclusions to be possible. It seems not unlikely that there will be found to be some non-specific tendency to congenital anomalies related more to the amount than to the nature of the chromosomal anomaly (mental defect being the most constant element), and a first task will be the identification, behind this screen, of more specific patterns related to disorders of individual chromosomes.

The demonstration in viable children of triploidy[22] or trisomy of three large chromosomes[21] at one end of the scale, and in normal individuals of trisomy[9] or translocations[7][8] at the other, shows that the human organism is not as sensitive to such changes as was once supposed. Every one of the twelve chromosome pairs of that old friend of the materia medica, *Datura stramonium*,[23] can exist in a trisomic form, and every one has its characteristic phenotype, or, as one calls it in medicine, its characteristic clinical syndrome. Perhaps we will soon recognise equally characteristic syndromes for each of our own twenty-two autosome pairs.

Tumours of the Bladder

IN the past decade the causes, treatment, and prevention of bladder tumours have aroused much interest. Fascinating questions surround the incidence of this disease. Why is it increasing in younger males? Why is it apparently commoner in towns than in the country? Why is it rare in Japan and India? Now that β-naphthylamine is no longer employed in the dye, chemical, or rubber industry, which industries still use carcinogens such as benzidine?

A possible cause of bladder tumours is the excretion in the urine of an abnormal metabolite of tryptophane. Some biochemists believe that this metabolite is hydroxykynurenin, others that it is hydroxyanthranilic acid or an allied compound. These chemicals can be suppressed in at least three ways: by administering pyridoxine, which alters tryptophane metabolism, or by administering saccharolactone, which inhibits enzyme activity in the urine, or by altering the urinary pH Whether it will be possible by chemical means to prevent so-called "recurring" tumours, which may, in fact, be new tumours due to the persistence of a carcinogenic stimulus, depends on whether the mucosal changes are reversible or whether, once the mucosa has been stimulated by a chemical carcinogen, neoplasia is inevitable even if the stimulus is removed Double-blind trials now in hand may provide the answer

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[8] Carter, C. O., Hamerton, J. L., Polani, P. E., Gunalp, A., Weller, S. D. V. *ibid.* Sept. 24, 1960, p. 678.

[9] Fraccaro, M., Kaijser, K., Lindsten, J. *ibid.* 1960, i, 724.

[10] Edwards, J. H., Harnden, D. G., Cameron, A. H., Crosse, V. M., Wolff, O. H. *ibid.* p. 787.

[11] Patau, K., Smith, D. W., Therman, E., Inhorn, S. L., Wagner, H. P. ibid. p. 790.

[12] Hayward, M. D., Bower, B. D. *ibid.* Oct. 15, 1960, p. 844.

[13] De Carli, L., Nuzzo, F., Chiarelli, B., Poli, E. *ibid.* July 16, 1960, p. 130.

[14] Sandberg, A. A., Crosswhite, L. H., Gordy, E. *J. Amer. med. Ass.* 1960, 174, 221.

[15] Jacobs, P. A., Harnden, D. G., Court-Brown, W. M., Goldstein, J., Close, H. G., MacGregor, T. N., Maclean, N., Strong, J. A. *Lancet*, 1960, i, 1213.

[16] Stewart, J. S. S., Sanderson, A. *ibid.* July 2, 1960, p. 21.

[17] Fraser, J., Campbell, J., MacGillivray, R. C., Boyd, E., Lennox, B. *ibid.* Sept. 17, 1960, p. 626.

[18] Jacobs, P. A., Harnden, D. G., Court-Brown, W. M., Baikie, A. G. *ibid.* Aug. 13, 1960, p. 368.

[19] Ford, C. E., Jones, K. W., Miller, O. J., Mittwoch, U., Penrose, L. S., Ridler, M., Shapiro, A. *ibid.* 1959, i, 709.

[20] Scandinavian cases cited by Fraccaro et al. (footnote 21).

[21] Fraccaro, M., Kaijser, K., Lindsten, J. *Lancet*, Oct. 22, 1960, p. 899.

[22] Böök, J. A., Santesson, B. *ibid.* 1960, i, 858.

[23] Swanson, C. P. Cytology and Cytogenetics, p. 188. London, 1958.

In the treatment of the established case one adverse factor that can be attacked is delay Patients often recognise hæmaturia as a symptom of possibly grave significance But this view is not always shared by the patient's doctor, who may treat painless hæmaturia, without associated frequency or pain, as a case of cystitis, and when the bleeding stops the patient and his relatives are lulled into a false sense of security In hospital, too, the possible gravity of the cause of hæmaturia is often not appreciated recently a patient with this symptom was given an appointment to be seen in the outpatient department three months later We accept pain in the right iliac fossa as a matter of urgency Why cannot hæmaturia be given similar priority? In cases of carcinoma of the bladder, when the delay between the onset of hæmaturia and treatment is less than a month the 3-year-survival rate is 70 5%, but when the delay is 6 months the 3-year-survival rate drops to 36 8%[1] Quick and accurate diagnosis is possible, and this is likelier to improve the results than any changes in the techniques of radical surgery or radiotherapy

In the past ten years surgery and radiotherapy have each held sway in turn Nowadays the limitations of surgery and the dangers of excessive radiotherapy are appreciated, the surgeon and radiotherapist work as a team, seeing, treating, and following up each case together This makes for better results—for example, in cases treated surgically in which metastases develop and require irradiation, and in cases treated by radiotherapy in which surgery is needed for resultant complications

Many factors, including the age and general condition of the patient, must be taken into account in treating bladder tumours When the disease is localised and confined to the mucosa the choice lies between intensive diathermy (either cystoscopic or open) or some form of radiation The complications of intracavitary radiation—contracted bladder, mucosal atrophy, and hæmorrhage—have led to its abandonment in such cases until better techniques can be evolved Diathermy—either electrocoagulation or electroresection—is therefore the method of choice The skilled surgeon can deal with even large tumours by this method, but this technique cannot be safely left to a junior For limited tumours infiltrating no farther than the muscle coat interstitial irradiation may be applied Formerly such tumours would have been treated by radon seeds, but nowadays artificially produced radioactive isotopes (gold or tantalum) are used This represents a technical improvement, for radioactive gold grains are smaller, safer, more accurately implanted, and obtainable in various strengths, while tantalum is relatively cheap, has a much longer half-life than gold, and can be kept at hand so that after cystoscopy the bladder can be opened, the tumour excised, and wire implanted at a single operation[2]

The supervoltage radiotherapy beam, directed either from generators, such as a linear accelerator or a Van de Graaf machine, or from artificially produced isotope bombs (telecobalt or telecæsium units), also has a place in treatment This therapy can render a bladder tumour-free, but sometimes it completely fails to affect the tumour Furthermore external radiotherapy in high dosage can produce radiation damage to the pelvic contents, including loops of small intestine These risks, though small, must be weighed against the possibility of cure and the chance of conserving a normally functioning bladder Using a linear accelerator at 8 MeV MORRISON[3] found that with a tumour dose totalling 4500–5500 rads in 4 weeks, 31% of patients had no tumour visible on follow-up cystoscopy There was a better response with the earlier tumours (mucosal tumours disappeared completely in 43%, and a further 19% became appreciably smaller) but the more advanced tumours also regressed in many cases These results show that supervoltage therapy is an extremely potent weapon and should be considered before recourse to radical surgery

Partial cystectomy has tended to fall into disrepute, largely because it has been employed in the wrong type of case MAGRI[4] has found that with single lesions, irrespective of the histological type (80% were solid anaplastic and infiltrating), where a clear margin of at least an inch was obtained there was a 71% 5-year-survival rate Where, however, the line of excision cut through the tumour or its submucous extensions there were no survivors after 5 years Partial cystectomy, though fairly easy, should be undertaken only after careful thought

Radical surgery following radiotherapy is not difficult provided that irradiation has not been applied over too short a time to too large a volume of tissue or in excessive dosage Radical cystectomy involves the removal of all the pelvic contents except the rectum, and also the lymph-nodes along the iliac vessels WALLACE[5] has found that this operation, undertaken after radiotherapy, as the last weapon in the therapeutic armoury, carries a mortality of 21%, but that it can prolong life by 3 or more years in half the cases of mucosal tumours, a third of the cases in which muscle is infiltrated, and a quarter of the cases in which the perivesical fat has been invaded

The treatment of bladder cancer is still far from satisfactory, but much can be done with our present resources to check the disease. It is heartening to know that a subcommittee of the International Union against Cancer has agreed on a provisional method of classifying and reporting cases, similar to that adopted for cancer of the breast.[6] If this recommendation is accepted the analysis of results should be greatly simplified.

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[1] Report from the Institute of Urology and Southern Metropolitan Cancer Registry

[2] Bloom H J G *Brit J Radiol* 1960 33 171

[3] Morrison R *Clin Radiol* 1960, 11, 125

[4] Magri J Personal communication

[5] Wallace D M *Brit J Radiol* 1960 33 187

Annotations

POMP AND CIRCUMSTANCE

THE ceremonial ward round has long been a familiar feature of our teaching hospitals. The Chief, surrounded by acolytes and disciples, proceeds in pomp from bed to bed, pausing now and then to correct a point of history, to confirm or deny the physical findings, to discuss the differential diagnosis, or to pontificate on methods of treatment. Ward-clerks and dressers stand around, shifting from foot to aching foot, bored registrars converse in whispers, nurses tiptoe past with bedpans, patients lie glum and silent while the Round drones on.

Is this the best way of teaching "bedside" medicine and surgery? The *Oxford Medical School Gazette*[7] thinks not. In a pungent editorial, entitled "Is Your W.R Really Necessary?", the *Gazette* reminds us that such methods are frequently discourteous and may sometimes harm patients. There the patient lies, sometimes half-naked, a forgotten object while the discussion rages over his bed. He is listening, moreover, with apprehension to the list of alarming investigations proposed for him, to talk of frightful-sounding diseases that he might have, sometimes to obvious differences of opinion about treatment. The more intelligent and educated he is, the worse his ordeal, for the more likely is he to glean from unguarded remarks some of the grimmer truths about his illness and to penetrate the thin veil of medical euphemisms. It is easy to forget that nowadays, thanks to television and other media of mass information, many patients have a smattering of medical terminology and jargon. And even if the Round removes itself a few beds away to discuss prognosis, other patients have ears, and ward gossip spreads. The physical suffering imposed on ward-clerks by the peripatetic ward round is a less serious matter, but they might listen better and learn more if allowed to sit down comfortably.

The *Oxford Medical School Gazette* suggests that all "bedside" teaching should take place in a room adjacent to the ward, with chairs, blackboard, and X-ray screen, into which patients can be brought when needed, or from which the Round can emerge for a brief visit to the bedside. This sensible idea has already been adopted by some teaching hospitals. We commend it to all. Such an arrangement has the additional advantage of ensuring that the formal "round" is recognised as purely for teaching purposes, as it should be, and is not mixed up with the day-to-day management of patients. It is impossible to teach properly on more than a few cases at a time. Practical therapy should be dealt with by the Chief later, when he goes round his beds privately with his junior staff. The traditional royal progress from bed to bed, with a gracious greeting and a few pearls of wisdom dropped at each one, may awe the impressionable but is not the best way either to teach clinical medicine or to cure patients.

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[6] See *Lancet* 1959 ii 958

[7] *Oxf med Sch Gaz* 1960 12 41

NEONATAL RESPIRATORY DISTRESS

RESPIRATORY distress in the premature infant is a common cause of neonatal death. Most of the affected infants have no evidence of congenital malformation or birth injury, hence they should survive if the distress could be prevented, and their recovery should be complete if it were more amenable to treatment. The challenge to obstetricians (for prevention of prematurity is the best means of preventing these deaths) and to pædiatricians is being met, and there is some encouraging progress to report.

In the past, research into respiratory distress has been largely concerned with the pulmonary and circulatory aspects.[1] This has proved less enlightening than was hoped, for the ætiology of pulmonary hyaline membrane remains obscure,[2] and the reported disturbances in the mechanics of breathing do not add greatly to our understanding, nor do they suggest any sound alternatives to present methods of treatment based on the administration of oxygen and nursing the infant in a humid atmosphere.

Interest has turned towards the biochemical changes associated with respiratory distress, and this may well prove a more productive approach. The present position has been well summarised by James.[3] Infants with birth asphyxia or respiratory distress become severely acidotic with hyperkalæmia, hypoglycæmia, and possibly hypocalcæmia. These changes are the expected consequence of anoxia and retention of carbon dioxide. They may well be responsible for death, and treatment with glucose, bicarbonate, and insulin holds out some promise of success.[4]

The maintenance of a stable blood hydrogen-ion concentration (pH) depends on the lungs and on the kidneys, and the newborn baby is unique in both pulmonary and renal function.[5] Some of the peculiarities of this period are now being elucidated. Helen Reardon and her colleagues[6] have reported the results of a technically brilliant investigation into the chemical aspects of the control of respiration in the early newborn period. They sampled blood not only from the umbilical vessels at birth but also from the temporal artery at various periods afterwards. They analysed the blood samples for plasma pH, CO_2 content, protein, O_2 content and capacity, and hæmatocrit. From these measurements the pCO_2, buffer base, and oxygen saturation were calculated. The results showed that the normal full-term infant is born with mild acidosis which is of both metabolic and respiratory origin. This is presumably due to an excess of fixed acids or deficiency of base which is uncompensated by hyperventilation. The rise in pCO_2 (respiratory acidosis) suggests that the birth process not only prevents compensation of the metabolic acidosis but leads to impaired CO_2 elimination. Within an hour of birth the respiratory component disappears owing to the efficacy of pulmonary ventilation, but the metabolic acidosis (decrease in bicarbonate or other buffer anions) tends to increase. There is thus a state of uncompensated metabolic acidosis. During the next few hours ventilation becomes efficient enough to compensate for the metabolic acidosis, and in some infants there is evidence of respiratory alkalosis. Correction of, rather than compensation for, the metabolic acidosis takes place in breast-fed infants from the 4th day but is delayed in premature infants Reardon et al argue that plasma-pH is the main stimulus to respiration because, during the phase of compensating metabolic acidosis, there is still increased respiratory drive in the presence of lowered pCO_2 and plasma-pH

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[1] Cook C D Barrie H Avery M E *Advanc Pediat* 1960 11 11

[2] See *Lancet* Nov 5 1960 p 1014

[3] James, L S *Pediatrics* 1959 24 1069

[4] Usher R *ibid* p 562

[5] See *Lancet* 1960 i 583

[6] Reardon H S Baumann M L Haddad E J *J Pediat* 1960 57 151

McCance and Widdowson[7] have shown that the kidney of the newborn infant secretes an acid urine at birth and in the first 48 hours of life, the acidity is due not to acid phosphates but to a predominance of ammonium salts and organic acids, and Zweymuller[8] has identified some of these as emanating from the citric-acid cycle Probably, therefore, the newborn infant depends greatly on pulmonary function for the maintenance of acid-base balance, when this function fails the metabolic sequelæ may be catastrophic, and perhaps the biggest change is the hyperkalæmia Whether this hyperkalæmia is due predominantly to renal retention of potassium and excretion of sodium or to the excessive liberation of potassium from within cells is uncertain It seems reasonable, however, to attempt to prevent the extrusion of potassium from the cells by adequate oxygenation and administration of glucose

PRISONS IN 1959

LAST year, as the annual report of the Commissioners of Prisons[9] relates, the numbers of prisoners grew yet again (though it fell in the autumn), and the numbers of prison staff increased in rather higher proportion, although many more are still needed New legislation had a rather greater effect on the prison population than usual, with a drop of civil prisoners from 744 to 265 due to the Attachment of Earnings Order and an extra 63 prostitutes under the Street Offences Act Imprisonments without fine continued to rise (by over 2500 to 28,411 for men) as did receptions of men not under sentence (by 1000 to 45,000) This means, as the commissioners say, that a regrettably large proportion of the effort of local prison staff is diverted from training persons convicted of crime For women this defect is even more evident, for only 47% of those remanded before sentence were given imprisonment, and some 85% of these were imprisoned for not more than six months There is a widespread feeling that some alternative must be found to short prison sentences, and the new Criminal Justice Bill published last week (its terms are summarised on p 1082) may lead to their abolition at least for young offenders The suspended sentence was buried in 1952, and the Advisory Council on the Treatment of Offenders in 1957[10] did nothing to disinter it The Council did, however, approve adult attendance centres and call for wide use of remand on bail for full inquiry between conviction and sentence, believing that the knowledge gained in this way would help magistrates to avoid giving imprisonment Lord Kilmuir[11] offered detention centres as an alternative for under-21s—a group of prisoners which increased enormously in 1959 (by over 700 to 2498) Nevertheless, for men, sentences of under three months and over three years are tending to diminish slightly and intermediate ones to increase

Regarding types of offence, convictions for violence against the person again increased, though this may only reflect changes in public attitude and sentencing policy Gordon Hawkins[12] has described grounds for believing that in the past half-century violent crimes have not increased significantly Sexual offences continued their downward trend, but not those against females Thefts of all kinds again increased, but imprisonment for drunkenness decreased (by about 200 to 3129) Heavy traffic and current anxieties about road deaths were doubtless partly responsible for the great increase in imprisonment under the Highway Acts—at 2627 the total last year was nearly 50% greater than in 1958 The views of Lady Wootton[13] and others are evidently making some impact on her fellow magistrates (Even so, the Royal Automobile Club[14] has pointed out that, while all traffic offences increased by 6 6% in the year, traffic volume went up by 10%) Local prisons, unfortunately, still carry the greatest load, holding about 4 prisoners to every 1 accommodated elsewhere Clearly " show " prisons such as Wakefield tell but a small part of the story

Breaches of discipline and escapes continued to cause concern Birching was ordered 11 times (3 in 1958), and this punishment was confirmed in 2 cases by the Home Secretary (0 in 1958) That 1 of these 2 men committed a second assault shortly afterwards must reinforce the belief that the value of corporal punishment is mainly to assuage the feelings of the staff In the contrary direction, however, the approach towards a " therapeutic community " proceeds The Norwich system of freer association between staff and prisoners continued to expand, and group counselling[15] spread to fourteen more prisons and borstals in the year Even at Dartmoor, this system has had a good reception Evening classes are expanding, but progress towards the realistic full-time work and reward system, so essential in training a man for ordinary life, is still disappointingly slow Nevertheless, an Advisory Council on the Employment of Prisoners has been set up, together with a new post of assistant commissioner (industrial) It is one of the anachronisms of the age that thousands of able-bodied men moulder away in gaols while public works, such as waterways and the decaying relics of the 1939–45 war, lie neglected But at least the pre-release hostel and training scheme is spreading as its success becomes more obvious Another means of reintegrating the offender with society is by home leave, over 300 borstal lads were thus paroled, and only 1 in 30 broke it

Detention centres remain one of the brighter hopes of the commissioners for coping with the " bulge " of moderately delinquent youth, and the new Bill seeks to make wider use of these centres But, despite great shortage of places, unsuitable lads—persistent offenders, the physically or emotionally disturbed, and approved-school failures—are too often sent to these centres, where they are not helped by the brief period of highly disciplined and energetic life, and where their presence has an adverse effect on others A better system of classification or of advice to magistrates is needed Whether this stern type of institution is more effective than milder methods has still to be shown by valid comparative techniques Over 50% of boys discharged in 1956 and 1957 had been reconvicted by 1960, and this does not sound too hopeful Aftercare, as the commissioners sadly note, is not yet compulsory, but the new Bill includes provisions for its extension to those coming out of detention centres

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[7] McCance, R A Widdowson E M *Acta pædiat , Stockh* 1960, 49, 409

[8] Zweymuller, E *ibid* p 591

[9] Report of the Commissioners of Prisons for the Year 1959 Cmnd 1117 H M Stationery Office Pp 199 9s 6d

[10] Alternatives to Short Terms of Imprisonment H M Stationery Office, 1957

[11] *Times*, Aug 9 1960

[12] *Criminal Law Review* October, 1960

[13] Wootton B Social Science and Social Pathology London, 1959 See *Lancet* 1960, i, 1238

[14] *Times*, Aug 10, 1960

[15] See *Lancet*, 1959, ii, 1015

Physical health in prisons remains good, and the trend towards using outside facilities continues, but the number found insane on remand jumped to almost double despite a decline in the number remanded for mental observation and report It is hard to explain these trends, perhaps the new outlook inherent in the Mental Health Act of 1959 may have permeated the prison medical services more quickly than it has influenced the judicial authorities

The prison services, avowedly therapeutic organisations these days, are under as much obligation as, say, the manufacturers of drugs to assess and to publish their results, particularly where new techniques such as group counselling are introduced In a recent lecture the Home Secretary [16] endorsed the views on research we put forward last year [15] It is therefore disappointing to find so little about new methods in the report In support of group counselling it includes a few staff impressions and a couple of letters from prisoners, only in an appendix is there some worth-while evidence—from a local prison where, despite a rising population, the Norwich system led to a drop in disciplinary reports of 131 to 369, and the continuing lapses were less serious than before Other than this, the cynic might be led to correlate the trend towards easier relationships in and out of the prison with the increase of indiscipline, escapes, and overcrowding which the report mentions A larger chapter on "Research" is needed in this valuable document The Home Office research unit, which is already doing a great deal, should stop hiding its light under a bushel Bricks and mortar may still be badly needed, but knowledge must be given a new priority

HUMORAL AGENT IN MIGRAINE?

BROADLY speaking, the mechanism by which symptoms are produced in an attack of migraine is agreed, but the exact changes in cranial blood-vessels and nearby structures which cause the characteristic head pains are still in dispute

Chapman et al [17] working on the hypothesis that besides local vascular change some inflammatory or pain-producing substance was produced locally, examined tissue-fluid from regions of the head which were tender during a migraine attack Specimens were collected by slowly injecting 2 ml of sterile physiological saline solution into the local subcutaneous tissue and then gently withdrawing some of it Controls were provided by taking samples from the scalps of migraine patients both during attacks and at other times, from people not subject to headache attacks, and from the subcutaneous tissue of the forearms of each subject In the headache subjects a substance was found which bioassay suggested was a polypeptide This substance, for which Chapman et al suggest the name "neurokinin", was present in small quantities in all specimens from all subjects, but very much larger quantities were found in tissue-fluid from the scalp of patients with headaches at the time the specimens were taken It was also found to be released into the segmental cutaneous tissue-fluid during dorsal root stimulation and in the axon flare reaction In one subject the substance was apparently reduced in amount after administration of ergotamine tartrate, and Chapman et al suggest that interference by ergotamine with an enzyme system liberating "neurokinin" from a plasma-globulin may be the basis of this effect

These results are extremely interesting They may possibly explain some of the longer-lasting features of migraine which apparently outlast the aura and headache But bioassay methods can be unreliable, and these findings will need to be confirmed and the substances if possible defined chemically

TUBERCULOSIS IN AFRICA

IN the first of the four Heath Clark lectures, delivered in London on Nov 2, Dr Charles Wilcocks traced the development of investigations into tuberculosis in Africa This disease, he said is still spreading, and drug treatment by itself is unlikely to provide the whole answer

Wide variations in incidence and mortality among different races, noted as long ago as the beginning of the century, had led Cummins to formulate his "virgin soil" theory According to this, primitive tribes were highly susceptible because, in the absence of the bacillus, they had never in their own surroundings been obliged to protect themselves against it, while those living in more urban communities had elaborated protective substances through contact with the bacillus The high tuberculosis incidence and mortality among African troops in Europe in the 1914–18 war seemed to support this theory, though subsequent workers had suggested that the troops involved had been in France for some time and that they broke down under stress in other words, that the cause lay more in the environment than in racial susceptibility

Between the wars extensive work by individuals and commissions, ably supported by administrators, led to an accurate assessment of the distribution and character of the disease It was found to be widely distributed and it progressed rapidly to death, with extensive cavitation and little fibrosis, and usually with involvement of both lungs The sputum was heavily infected, and this was clearly a factor in spread when the patient and the rest of his family slept together in small, poorly ventilated houses

Some idea of the distribution of the disease could be gained from the large proportion—41%—of the total health expenditure of the Union of South Africa devoted to tuberculosis In the mines pneumoconiosis had added to the problem, although more careful selection of recruits and measures to cut down dust had reduced the number affected

Treatment, previously limited to bed rest and an occasional pneumothorax, had been radically changed by the advent of effective drugs But these might fail to control the disease, especially if the patient was not treated in hospital, because many did not take *p*-aminosalicylic acid with their isoniazid, and others stopped treatment before they should Thus resistance developed on a large scale

B C G vaccination was sometimes the only rapidly applicable preventive measure, and its value was probably small But these were short-time measures For widespread improvement, the attitudes of members of very different cultures had to be modified and research undertaken into the means of persuading whole communities to change habits which favoured the development of tuberculosis The most pressing need was improvement in environmental conditions The emphasis had now shifted to stress as the main causal factor in tuberculosis Nutrition, housing, working conditions, and hygiene and sanitation all required attention The £10 million per annum spent by the South African Government in the past five years on housing for non-Europeans was a step in the right direction It was unfortunate that the World Health Organisation, in its last report on the subject, had barely touched on the environmental factor, presumably because it was considered self-evident But anything which was not mentioned tended to be forgotten

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[16] Penal Reform and Research By R A BUTLER Liverpool University Press 1960 Pp 14 3s 6d

[17] Chapman L F, Ramos A O, Goodell H, Silverman, J, Wolff, H G *Arch Neurol* 1960, 3 223

It was the doctor's duty to stimulate the administrators to improve conditions, just as had been done in England a century ago

A SEX-LINKED FAMILIAL PURPURA

THE classical sex-linked hereditary bleeding diseases are hæmophilia and its close relation, Christmas disease In the past six years there have been reports of a purpuric hæmorrhagic disorder with a similar mode of inheritance by a sex-linked recessive gene—i e , the condition affects males but is transmitted by female carriers who are unaffected, and each male has an equal chance of being affected or free The condition, first described in 1954 by Aldrich et al ,[1] presents the odd combination of thrombocytopenic purpura, eczema, and undue liability to infection In the family, of Dutch extraction, observed by Aldrich et al , the male infants were known to be liable to die in the first few years of life with " draining ears, eczematoid dermatitis, and bloody diarrhœa ", in the last three generations 16 out of 40 males had died with this disease before the age of 31 months Krivit and Good [2] investigated the same family in 1959 and found that there were 2 female carriers who were reproducing, and that these had had 8 children since 1954, 2 were healthy girls and 6 were boys, of whom 3 had the disease and 3 were healthy

2 cases in an English family have now been reported by Gordon,[3] of Sheffield He points out that seven families affected by the disease have been described, one of them a Negro family Details of 16 male patients are known, and all have died, 1 of Gordon's patients has died, and 1 is still alive

Gordon's 1st patient was admitted to hospital at the age of 14 months with infantile eczema affecting the head, neck, arms, and legs A bleeding tendency had been noted from the age of 4 months, and this had alarmed the mother because she had had a brother who had died of " hæmophilia " at the age of 1 year Investigation showed severe thrombocytopenia, which persisted except for short periods when the count rose above 100,000 per c mm Bone-marrow was found to contain platelet-forming megakaryocytes With treatment the eczema improved, and the patient was sent home He was in hospital again on account of eczema five months later, and at the age of 4 years he was admitted with profuse purpura, bleeding gums, discharging ears, and impetigo The thrombocytopenia being still present, it was decided to carry out splenectomy, and this was followed by a rise of platelets to normal and disappearance of the purpura But in the next twelve months the patient had to be admitted three times—once because he had meningitis due to pneumococcal and staphylococcal infections, once for dental extraction which caused no trouble, and finally in a fatal coma Necropsy showed bilateral adrenal hæmorrhages, there was no evidence of septicæmia, the platelet-count was not recorded

Gordon's 2nd case was the brother of his 1st patient, born eight years later, in between, a healthy girl and a healthy boy had been born This 4th child of the family showed eczema at the age of 3 months, and a month later he was investigated in hospital, he had thrombocytopenia, and furunculosis, pyuria, and bronchitis developed while he was in hospital His white-blood-cell count was normal, and he did not have deficient γ-globulin Treatment with prednisolone and then with corticotrophin produced only a temporary rise in the platelet-count In view of the experience with the elder boy splenectomy was not performed, and the patient has remained reasonably well for three years, still having occasional purpura and occasional attacks of respiratory-tract infection

This syndrome will be easily recognised, though we have no doubt that children with eczema and thrombocytopenic purpura will be seen who do not have the syndrome, the added features of recurrent infection and, above all, a positive family history must also be found The cases so far reported have not been very fully investigated Krivet and Good sought platelet agglutinins but did not find them, marrow punctures have shown the same picture as that of " idiopathic " thrombocytopenic purpura, γ-globulins appear normal But nothing is known about the other blood-clotting factors No attempt seems to have been made to find out whether the condition is linked in any way with systemic lupus erythematosus and similar diseases, in which thrombocytopenic purpura is sometimes an early sign We hope that pædiatricians will look out for cases of Aldrich's syndrome and see whether more can be learnt about its ætiology and possible lines of treatment

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[1] Aldrich R A Steinberg A G , Campbell, D C *Pediatrics* 1954, 13 133

[2] Krivit W Good R A *A M A J Dis Child* 1959 97, 137

[3] Gordon R R *Arch Dis Child* 1960 35 259

CHEMICAL MENINGITIS FOLLOWING SPINAL ANÆSTHESIA

FORMERLY, when measures were not taken to avoid contamination of the subarachnoid space with phenolic disinfectants, chemical meningitis was a recognised sequel of spinal anæsthesia [1] Sterilisation by autoclaving of special packs containing all the equipment, including the ampoules of local anæsthetic, required for this form of anæsthesia is now commonly practised to prevent this complication But autoclaving by itself is inadequate if the syringes and needles have not been previously freed from all traces of disinfectant by cleansing and washing

The dangers of inadequate washing of equipment are well brought out in an account of five patients in whom acute meningitis developed very shortly after spinal anæsthesia for obstetric delivery [2] The cerebrospinal fluid in each case was purulent, with a polymorph leucocytosis These findings, together with pyrexia, suggested bacterial infection of the subarachnoid space, but no organisms could be isolated from the cerebrospinal fluid or from blood samples A review of the procedures used for cleansing spinal anæsthetic equipment in the obstetric department concerned revealed that, whereas the ampoules of local anæsthetic were taken directly from their carton before autoclaving, the syringes used were soaked in a solution of a phenolic disinfectant, washed and rinsed, and finally put in trays ready for autoclaving Clearly this washing was ineffective Fortunately, all five patients recovered without permanent neurological sequelæ Their illnesses illustrate once again the dangers associated with this mode of anæsthesia when insufficient precautions are taken to avoid contamination of the subarachnoid space

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[1] Rendall C M *Anæsthesia* 1951 6 281

[2] Goldman W W Sanford J P *Amer J Med* 1960, 29 94

Points of View

FUTURE ROLE OF THE FAMILY DOCTOR*

E. MAURICE BACKETT
M.B., B.Sc. Lond., M.R.C.P., F.S.S., D.P.H.
PROFESSOR OF SOCIAL MEDICINE IN THE UNIVERSITY OF ABERDEEN

WITH the changing patterns of disease in Western societies, particularly the emergence of the chronic diseases (heart-disease, cancer, peptic ulcer, bronchitis), of accidents (especially motor-vehicle accidents), and of the multiple effects of radiation as the characteristic and newly important threats to the public health, there has come the possibility of a rather different sort of medical care. This new approach is preventive in attitude (though the borderline between prevention and very early treatment is rapidly becoming meaningless). It is preventive in the sense of using our growing epidemiological knowledge accurately to define vulnerable groups, families, and individuals in our population and of manipulating their personal and social environment to prevent disease. But the differences between the present and future preventive medicine are more important than they seem at first sight. These days (and at long last) most of us accept the necessity for clean milk and the quality control of food, for example, without demur. These controls are, for the most part, satisfyingly impersonal. But just let us try advocating changes in the individual and family dietary customs of the healthy rather than the sick in our practices, or their leisure pursuits, or try to change one of many minor addictions to which we are all prone, and we are in for trouble. That trouble is made subtly worse by a sneaking feeling that we may have no right to meddle in these personal matters anyway, and that our techniques, if we do, are naïve. Yet, if the future general practitioner is to attempt the control of chronic disease in his practice, he has little choice—he *must* meddle, and his meddling must be increasingly personal, for it seems very likely that before long our so-called "new" diseases will offer as much of a threat to life and happiness as did some of the epidemics of the 19th century. And, since many of these diseases have their origins in our changing ways of living, a tolerable amount of interference may help to prevent them.

By "new" diseases I do not mean only novelties but *newly important* diseases which, because of their increasing contribution to our morbidity and mortality, must be counted as new threats. For example, with the decline (but not the defeat) of the infections we can see more clearly the enormity of our chronic-bronchitis problem (25 million man-days lost per year, and thousands of deaths), of our cancer problem (100,000 deaths per year), of heart-disease, and of chronic but not always fatal diseases like diabetes and multiple sclerosis. We see, too, the useless (though fortunately small) waste of fœtal and neonatal life and the few remaining maternal deaths in a new context: the context of a society which, perhaps unlike all previous societies, does not expect illness and early death and which thinks of health and happiness as its right.

* * *

We can summarise the main features of our changing disease patterns in this way. First, the *vulnerable age-groups* are shifting. Young people are seldom ill. In fact the older children and adolescents have virtually disappeared from the doctor's surgery. There is increasing emphasis on the intrauterine child and the neonate, rather than the infant. Then there is the new interest, of course, in the elderly, and above all a growing anxiety about the middle-aged. The *sex ratios*, too, are changing, and the new diseases are increasingly selective of males.

Next, the *type of disease* is changing (and, inevitably, our attitude towards it). For example, infectious disease outbreaks are often spectacular and explosive, cases occur near one another, a hundred or so deaths in a small community has the impact of disaster, while the same number of deaths spread over the whole country—motor-vehicle or coronary deaths, for example—does not carry the same provocative danger signal. Some catastrophe is needed to promote social action.

Next there is the *duration of illness*. Most of our new diseases are chronic slow-moving processes which may take many symptomless years to develop. We are told that the cancer of the lung, for example, may have started fifteen or twenty comparatively healthy years before the first symptom of the disease, and that the men now dying of chronic bronchitis may well be reflecting not only their smoking habits and the air pollution of the cities in which they have lived but also the shorter convalescence enforced on working-class families by the tough economic pressures of the hungry '30s. It is, perhaps, this very long duration of our chronic diseases and of cancer which is doing most to force us to review our methods of medical care.

Finally, we can say that with a few exceptions our new threats to health seem, by their very nature, somewhat less likely to respond to curative medicine than the diseases of the past. However, this point is not a strong one, and, to strengthen the case for a review of our preventive measures, I would say that, thanks to the impeccable epidemiology of people like Doll, Case, and Morris, the prevention of many cancers (and some other chronic diseases) is becoming possible long before the disease itself is fully understood. Thus, in the face of our new diseases, *prevention* acquires a new urgency, and the wise family doctor is being forced increasingly to switch his attention from sick people to the habits and behaviour of healthy people many years before the clinical onset of illness.

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So here, very crudely, is the problem. Most people who feel ill seek medical care and have a rather special relationship with their doctors. Healthy people, on the other hand, are unlikely to be particularly impressed by talk of a disease which *may* come in twenty years' time. Their replies to doctors who seek to change their behaviour, and thus to promote their future health, are polite but negative.

The dilemma is most acute for the family doctor, for it is now becoming technically possible for a large part of his job to be the highly scientific supervision of healthy people. Indeed, this looks like being the only way to cope with our new diseases. Such a statement does not sound particularly surprising, but at the moment well over 90% of the family doctor's work with adults is curative, dealing with established disease. If even a quarter of his work were to be concerned mainly with healthy people, rather than the sick, this would be a revolutionary change—at least as revolutionary as was his assumption of the role of vaccinator and immuniser of children Such a change has been made *necessary* by the changes in our disease pattern, and *possible* by a growing knowledge of the reasons for variation in the vulnerability of different age, sex, and social groups This means that the doctor who really knows how his patients live will be able to define with increasing accuracy who is likely to become ill In fact, he alone—because of his contact with the family—can become the man to observe those aspects of behaviour which we suspect are the precursors of much chronic disease

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* Abridged from a paper read to the sociological section of the British Association on Sept. 2, 1960. The full text will appear in *Advancement of Science*.

As a help toward the practical application of this change of approach, the doctor now has a growing armoury of screening devices and simple tests by which he can pick the already ill from among the merely vulnerable people in his practice, and so make earlier and ever earlier diagnoses Many of these screening tests are sensitive enough to be used while the patient is still feeling fit—that is before he would normally seek medical care, and long before serious symptoms arise

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These notions may be illustrated briefly by reference to cancer of the uterine cervix Epidemiologically speaking, this cancer is well described A lot is known about what sort of people get it (but, of course, very little about how they get it) Through relatively simple technical advances it is becoming possible to make increasingly early diagnoses of the developing growth We are told that treatment at an early stage is relatively easy and safe, but that the diagnosis must be made before the symptoms and signs develop We are also told that the test is rapidly achieving real accuracy So it is this combination of good epidemiology (which could guide the doctor to where the disease will arise—so that he need not screen all the women in his practice) and this early test which has suddenly given the family doctor the power if not to eradicate the disease then perhaps drastically to reduce it in his practice But, at once we are back with the same problems as before How to persuade apparently healthy women who belong to the vulnerable age, parity, and social group to seek medical care long before they feel ill, how to persuade the doctor to persuade them, and finally, how to fit this approach into a service and a society quite naturally preoccupied with curative medicine

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Tests which can be used for screening apparently healthy populations for all manner of different diseases are rapidly increasing in number and accuracy They are an exciting product of the growing gadgetry of medicine Already it seems probable that more or less accurate and very early diagnoses (that is, long before the patient is conscious of illness) can be made in a variety of chest conditions, a few cardiovascular disorders, some renal diseases, and an assortment of hereditary metabolic upsets, mild diabetes, and at least one cause of blindness

In this way it seems that our new diseases are themselves forcing us into at least the contemplation of a different sort of medical care This medical care may in turn need a rather different sort of doctor to apply it Such a man would have different interests and would need much more time than today's family doctors whose hospital education very properly emphasises curative medicine above all else

There are other difficulties apart from those of time and interest For example, most doctors feel that, at least at first, we should play a passive waiting role the initiative obviously should be with the patient With this in mind most of us would find it very difficult, for example, to write to a lot of healthy adults on our lists inviting them to undergo even the simplest of screening tests It would be even more difficult to go to the length of reorganising our practices so that much of our time was spent in this way

There is yet another problem How could the future family doctor screen the vulnerable people on his list, offer his genetic counsel, advise effectively on diet, exercise, and so on, or even check the blood-pressure and weight of the paunchily middle-aged (if one day it is agreed that these too are useful screening tests) without creating not a healthy practice but a practice of neurotics? We have seen a suggestion of this mass fear of illness following the indiscriminate "check-up" campaigns, the cancer films, and the commercial exploitation of anxiety which has occasionally been a feature of "health education" elsewhere Our small experience of studies over here, and the wider experience of calmly and well run studies of community health (such as that at Framingham in the U S A), suggest that these dangers can be avoided But they remain an important threat, and the prevention of some heart-disease, for example, might save the lives of mentally healthy men at the cost of converting them into cardiac neurotics

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Changes in disease patterns must always have given rise to new social problems our current transition from *the infections to chronic degenerative disease is* obviously no exception The changing role of the general practitioner is among the most intriguing of these problems, and it may be that in future he will have to be prepared to make himself more of a nuisance to his patients But if he does, will they take any notice of him—and why should they anyway?

Public Health

Infectious Diseases in England and Wales

Disease	Week ended October				
	1	8	15	22	29*
Diphtheria	4	3	4	4	
Dysentery	477	500	600	465	581
Encephalitis					
Infective	1	3	4	2	3
Postinfectious	3		2	2	
Food poisoning	287	225	188	181	196
Measles excluding rubella	996	2856	3220	3917	4585
Meningococcal infection	19	28	29	19	18
Ophthalmia neonatorum	21	16	24	31	9
Paratyphoid fever	6	7	12	4	7
Pneumonia primary or influenzal	175	202	239	213	221
Poliomyelitis					
Paralytic	12	14	8	10	13
Non paralytic	6	4	7	1	2
Puerperal pyrexia	153	194	201	188	171
Scarlet fever	305	357	424	465	409
Smallpox					
Tuberculosis					
Respiratory	387	386	428	436	343
Meninges and C.N.S	2	2	2	2	6
Other	48	44	47	57	51
Typhoid fever	5	4	1		3
Whooping cough	1110	1021	931	860	964

* Not including late returns

Special Articles

EAST-WEST SYMPOSIUM ON PATHOGENESIS OF ESSENTIAL HYPERTENSION*

CLIFFORD WILSON
D.M. Oxon., F.R.C.P.
PROFESSOR OF MEDICINE, UNIVERSITY OF LONDON,
DIRECTOR OF THE MEDICAL UNIT, THE LONDON HOSPITAL, E.1

"ALTHOUGH it appears that essential hypertension is a widespread condition and a frequent cause of premature invalidism and death, there is little agreement about its pathogenesis or about the role of various environmental factors in its production. This lack of knowledge prohibits any rational attempt at prevention. It seems desirable, therefore, to discuss the conflicting views and to delineate fields in which future research might possibly be concentrated with profit."

These were the broad terms of reference of a symposium which was held in Prague early in the summer under the joint auspices of the European Region of W.H.O. and the Czechoslovak Cardiological Society. Some 40 workers, engaged in research on various aspects of hypertension, attended, chiefly from the U.S.A., U.S.S.R., and Great Britain, but almost every other country in Europe was represented.

The detailed proceedings of the conference will be published shortly, and these will include an account of individual papers and the variety of opinions expressed in discussion. Nevertheless it seems worth while to record some personal impressions now which it is hoped may give some idea of the positive achievements of the symposium. Research on hypertension has recently received a fresh stimulus from several different directions, and this was reflected in the lively controversy and some new ideas which found expression during the symposium.

One stimulus in Prague was undoubtedly the opportunity of hearing from Russian investigators about their concept of essential hypertension as a specific neurosis, against the experimental background of hypertension induced in animals by nervous or emotional strain. New interest has also been aroused by epidemiological studies on the role of genetic and environmental factors, one outcome of which is the current controversy on whether essential hypertension is a disease entity or a biological variation differing only quantitatively from the normal. Furthermore, the widespread use of hypotensive drugs with a variety of pharmacological effects has not only emphasised the need for a clearer understanding of the fundamental nature of the disorder, but has also produced some new ideas about possible mechanisms in its pathogenesis. In the investigation of these problems, statisticians, physiologists, experimental pathologists, and pharmacologists are becoming increasingly active. The old controversies about humoral and neurogenic mechanisms have been given a new look by the discovery of intriguing relationships between renin and aldosterone, by more critical assessment of the role of catechol amines, and by the researches of neurophysiologists in several countries on the nervous regulation of the circulation. Added to this is a questioning of the old concepts of the hæmodynamic status in hypertension in which circulatory changes were accepted as incidental to a primary increase in peripheral resistance, so that the search for ætiological factors was focused almost exclusively on this restricted part of the vascular system.

The symposium was arranged as a series of discussions on the following topics: definition, diagnosis, and natural history, epidemiology, the role of emotional and environmental factors, neurogenic factors in the control of blood-pressure, hæmodynamic studies in essential hypertension, vessel-wall factors, metabolic factors, including the possible role of pressor amines, the adrenal cortex, and the kidney.

Although there was considerable divergence of opinion on most of the topics discussed, there was a fair amount of agreement on the nature of the problems which need to be tackled. These I have attempted to summarise in the following questions:

(1) In the light of modern knowledge, can we arrive at any more satisfactory definition of essential hypertension than the present one of "elevation of the blood-pressure without apparent cause"?

(2) In view of the more exact methods of diagnosis now available, how large a proportion of cases, masquerading under the diagnosis of essential hypertension, are really due to some local disease—e.g., of the kidneys or endocrine glands?

(3) Is it possible to find a means of separating normal from high blood-pressure, not only in the numerical sense, but also in establishing whether essential hypertension is qualitatively different from the physiological range of the blood-pressure?

(4) How valid are casual blood-pressure readings, especially when used as an index in epidemiological studies? How far can such blood-pressure readings be standardised?

(5) How large a part does heredity play in the pathogenesis of essential hypertension? Is the genetic factor sufficiently large to indicate a primary metabolic fault in blood-pressure regulation as the main cause?

(6) What is the role of environmental factors such as geographical situation, diet (including electrolyte intake), occupation, and particularly, mental strain or emotional stress?

(7) Does the blood-pressure rise with age uniformly in the population as a whole, or is there an excessive rise in a limited group, who as they get older emerge from the normal population owing to the development of a specific disease, essential hypertension?

(8) How often does "transient" or "intermittent" hypertension lead to established hypertension—i.e., is there a definite sequence in the natural history from transient to permanent elevation of the blood-pressure?

(9) Can a prehypertensive state be recognised in which metabolic or vascular responses may make it possible to anticipate the development of essential hypertension?

(10) What part do nervous, renal, and endocrine mechanisms play in determining peripheral vascular resistance? Is there any real evidence that these factors play a different role at different stages of the disease?

(11) Is the regional distribution of increased peripheral resistance the same in all cases? Is it different in the early and late stages, and does it differ from the distribution in other hypertensive disorders such as renal hypertension?

(12) Is it possible that, with advancing age, some alteration in the vessel wall may produce a change in reactivity to physiological stimuli?

For the various topics in the symposium, discussion leaders were appointed, and produced a day-to-day progress report. In the final discussion on "topics and future trends for research arising from previous discussions " an attempt was made to coordinate the results of the conference, particularly with a view to international co-operation in various fields. In what follows, I have tried to give a brief account of the general conclusions on the various topics seriatim, but it must be recognised that on some issues there is still considerable disagreement on both the validity and the interpretation of the available evidence, or on its relevance to essential hypertension.

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* This article is based on a summary review of the symposium presented to the Czechoslovak Cardiological Society, and a lecture on experimental hypertension to the Czechoslovak Nephrological Society, Prague, June, 1960.

Definition and Natural History

On the question of *definition* it was generally agreed that at present there is no satisfactory alternative to the term essential hypertension, indicating " a common form of high blood-pressure without apparent cause ". Whilst modern diagnostic techniques are revealing increasing numbers of cases due to specific lesions, such as renal-artery stenosis, pyelonephritis, or endocrine disease, this is almost certainly a minority group—not large enough, for example, to invalidate epidemiological studies based on measurements of blood-pressure as the sole criterion. In the individual it is impracticable to define a critical dividing-line between normal blood-pressure and essential hypertension; but this is equally true of other forms of hypertension—e.g., that due to renal disease. Whether essential hypertension is a disease entity, qualitatively different from the physiological range of blood-pressure, may well be decided by a critical analysis of existing epidemiological data, together with further planned investigation of selected populations. If indeed we are dealing with a specific disease, some biochemical fault should eventually be discovered. There is evidence that patients with essential hypertension do show qualitative differences from the normal—for example, rapid electrolyte diuresis following plasma-volume expansion by a water or solute load, reversal of the normal antidiuretic effect of injected angiotensin, and the recent evidence of increased secretion of aldosterone in malignant hypertension—but it has yet to be shown that these differences in behaviour are specific for essential hypertension and that they are primary rather than secondary manifestations.

One of the most urgent needs is a clearer definition of the *natural history* of the disorder. Physiologists, experimental pathologists, and epidemiologists are tending to interpret their various data in terms of the " early " or " late " stages of the disease, but there is as yet no clear understanding of these stages or indeed of the relationship of transient to established hypertension. It may well be that further clarification of the natural history will emerge from characterisation of the various states (if these exist) by biochemical or physiological tests. Thus, response to salt-loading or angiotensin, or differences in secretion, utilisation, or end-organ response of adrenal cortical hormones, may be found to differ in different clinical groups; or again there may be a change in hæmodynamic pattern in terms of cardiac output and distribution of regional resistance. Possibly nervous and humoral factors play different roles in the early and later stages. We know, for example, that a minority of cases, especially in young subjects, have an increased cardiac output. Whether this is due to anxiety at the time of the investigation and whether it can still be demonstrated after hypertension has persisted for many years needs to be determined. Whilst some of these questions—e.g., a better definition of stages of the disease—may be answered by large population studies, most of them will require long-term and more detailed investigation of small numbers of patients by the clinician and experimentalist working together. For, apart from problems of differential diagnosis, it will be essential to recognise the intrusion of secondary factors, such as local atherosclerosis, altered renal function, or emotional reactions, which may modify the physiological pattern and bring into play new homœostatic mechanisms.

Epidemiology

The starting-point of epidemiological studies is the validity of blood-pressure estimation as an index. Examination of the " casual " blood-pressure should be made to see whether further standardisation of technique is possible and what additional criteria can reasonably be included in population studies. The epidemiologist is on uncertain ground until the validity of the high casual pressure as an indication of essential hypertension is assured. But if this can be established, some of the really fundamental problems of ætiology may be solved by epidemiological methods. The most important of these is *heredity*. If the genetic factor in essential hypertension is of major importance there is an urgent need to seek for an inborn error of metabolism in the pathogenesis of the disease. Even if there is a specific genetic factor, the environmental situation may well determine whether this defect leads to manifest disease. Furthermore a distinction (commonly overlooked) must be made between genetic factors and the " cultural inheritance " which is also transmitted in the family. The influence of *age* is the second main problem which epidemiological studies should be able to resolve, for if a substantial rise in blood-pressure can be shown to develop in a discrete section of the population as age advances, in contrast to little or no rise in the remainder, there can be little doubt that essential hypertension exists as a separate entity; furthermore the search for a causal mechanism can then be directed to changes in function with advancing age. There is a good deal of evidence, at present difficult to evaluate, of blood-pressure differences between population groups, which may be related to ways of life. It is in the epidemiological field that international cooperation is likely to be most fruitful, particularly in the investigation of racial factors, the effects of diet, the stresses of industrialisation, and other circumstances where differences in prevalence, already recognised, present " experiments of opportunity ".

The Neurogenic Hypothesis

The view that essential hypertension has a neurogenic basis is undoubtedly enjoying a new wave of popularity. Investigators in the Soviet Union have for some years maintained that essential hypertension develops as a specific manifestation of neurosis, and this has led to observations on the prevalence of hypertension in different occupation groups, to extensive physiological researches on the nervous regulation of the circulation, and to studies in dogs and monkeys of experimental hypertension produced by stress stimuli using conditioned reflexes and Pavlovian techniques. The widespread use of hypotensive drugs which act centrally or peripherally by inhibiting autonomic vasoconstriction has produced in some quarters an uncritical acceptance of the neurogenic theory, or at any rate of an important nervous component in essential hypertension. Supporting evidence has been sought, particularly in the United States, by analysing the emotional and hæmodynamic responses of hypertensive individuals to stressful situations, or by studying cultural background, character structure, and behavioural patterns in relation to the incidence of the disease Owing to lack of translations of published data it is impossible to give a fair assessment of the Russian view, and it is to be hoped that the clinical, experimental, and epidemiological evidence on which this concept is based will soon be made more readily available At present most workers agree that in the established phase of essential hypertension—i e, when the diastolic pressure is persistently raised—there is no convincing evidence that the cause is neurogenic vasoconstriction That emotional stress can cause acute elevation in blood-pressure is undoubtedly true, but the relevance of this to the chronic disorder we term essential hypertension is quite obscure, and in neither transient nor established hypertension has increased autonomic activity been demonstrated by the finding of increased catechol-amine production, as is observed in patients with high blood-pressure due to phæochromocytoma There is obviously a need for a more critical and broadly based assessment of hypertension of supposedly nervous ætiology in terms of its clinical characteristics, hereditary origins, and subsequent course Furthermore when studying emotional responses in both personal behaviour and vascular reactivity, it is essential to establish to what extent these are the cause or the result of the elevated blood-pressure

Hæmodynamic Changes

From what has been said it will be obvious that the largest single obstacle to understanding the genesis of hypertension is an imperfect knowledge of the factors which control the blood-pressure in health It would be easier to decide whether hypertension was " abnormal " if we understood better the mechanisms by which normal blood-pressure is maintained This becomes even more obvious when considering the further problems of hæmodynamic changes, vessel-wall factors, and the possible role of renal and endocrine dysfunction in essential hypertension In the field of blood-pressure regulation, physiologists seem to have been until recently almost exclusively concerned with the autonomic control of vascular tone In various discussions a great deal was heard about the baroceptors and other vascular receptor mechanisms, about cardiovascular changes following hypothalamic stimulation, and about the central and peripheral effects of hypotensive drugs on autonomic status and catechol-amine production It is well established that the response threshold of the baroceptors is raised in chronic hypertension, but this appears to be an adaptation to the high blood-pressure rather than its cause Recent physiological and pharmacological work has certainly revealed new aspects of neurogenic control of the circulation, but those who are concerned with the problem of hypertension, either clinically or experimentally, are questioning the adequacy of this approach, and are seeking information on other possible regulating mechanisms which may be more relevant in maintaining blood-pressure at a high level For example, what controls the residual arteriolar tone when all sympathetic influences are removed? Is it some endocrine factor, a renal pressor substance such as angiotensin, or is it a question of the electrolyte environment of the smooth-muscle cells of the arteriole? Whatever the controlling factors, vessel tone varies under the influence of a number of stimuli, and this brings up the vexed question of vascular reactivity Pressor responses to vasomotor stimuli such as cold, emotion, and vasoconstrictor drugs have so far failed to provide a convincing separation of hypertensive from normotensive subjects or to predict the future development of high blood-pressure in the latter Yet the level of the blood-pressure alone is insufficient to explain individual differences in the production of both functional and structural vascular reactions—e g, hypertensive headache, papillœdema, fibrinoid arteriolar necrosis and localised cerebral vasoconstriction in hypertensive encephalopathy

In general the view has long been accepted that narrowing of the arterioles is the primary hæmodynamic change in essential hypertension An alternative view is that vasoconstriction may occur as a reaction to increased intra-arterial pressure, which might be caused, for example, by a rise in cardiac output This possibility has directed attention to primary changes in cardiac dynamics and to possible alterations in venous tone or venous blood-volume, which might affect cardiac output and thereby initiate arterial hypertension Deviations from normal behaviour, such as the rapid salt diuresis in chronic hypertension, and the link between reduction in plasma-volume and blood-pressure after administration of diuretics such as chlorothiazide, have suggested a disturbance in the relationship between vascular capacity and blood-volume in the hypertensive patient Various new and interesting techniques are being developed in an attempt to explore these possibilities Methods have been devised for a more exact physical analysis of the parameters of vascular tone, and it is hoped that these may provide a means of identifying and assessing the effects of neurogenic and humoral factors, and of vascular " reactivity ", in hypertension of various sorts Hæmodynamic studies on cardiac output, and on the regional distribution of peripheral resistance, suggest that in hypertension certain areas of the vascular bed—e g, the kidneys and skeletal muscle—respond differently in different circumstances Experimental models are also being devised in animals in an attempt to separate the cardiac component from the role of the peripheral circulation during changes in blood-pressure induced by various means

Metabolic Factors

The symposium included a number of papers and a very critical discussion on the role of pressor amines, the adrenal cortex, and renal factors in the pathogenesis of essential hypertension Most workers agreed that at present there is no direct or convincing evidence that either the kidney or the endocrine system plays a part in the early or later stages, although this may not be true in the malignant phase of the disease Here again we are faced with the problem of distinguishing primary factors from secondary changes which develop in severe hypertension as a result of renal vascular damage Such damage may produce metabolic disturbances—for example, in sodium and water excretion—and may possibly alter the pattern of hormone production (e g, hyperaldosteronism in malignant hypertension) Nevertheless recent work on the reciprocal action of renin and aldosterone, and on the relationship of renin production by the juxtaglomerular apparatus to renal perfusion pressure, have produced, if not yet a promise, at any rate a hope, of a clearer understanding of renal participation in blood-pressure regulation

There is another line of approach, based on both clinical

and experimental observations, which is certainly relevant to the problem of chronic hypertension in general, and possibly by analogy to essential hypertension This is the growing evidence of a change in mechanism when high blood-pressure passes from the acute to the chronic stage Thus when hypertension is caused by some specific lesion—e g , phæochromocytoma, adrenal cortical tumour or unilateral renal disease—the pressure frequently remains elevated when the primary cause is removed As far as present evidence goes, it does not seem possible to distinguish this chronic residual hypertension from essential hypertension on clinical, physiological, or anatomical grounds There is some evidence also of a difference in mechanism between the hypertension of acute and chronic nephritis and early and late experimental renal hypertension These observations underline the importance, first, of looking for a similar change in mechanism in the development of essential hypertension, and, second, of considering the possibility of a common factor in the various forms of chronic high blood-pressure The striking thing is that in all these conditions a new equilibrium appears to have been established at a high level of blood-pressure which is consistent with many years of good health This would appear to involve a " resetting " of the homœostatic mechanisms which normally maintain arterial pressure at a steady level There is evidence of such a resetting in the case of the baroceptors, but, as already mentioned, the evidence does not suggest that this is of causal significance One of the most clear-cut observations in this field is the reversibility of chronic renal hypertension In the laboratory animal, renal hypertension of long duration is reversed within a matter of hours if the renal circulation is restored to normal In man a similar prompt reversal of chronic renal hypertension has been demonstrated when, in identical twins, a normal kidney has been grafted in a twin with chronic nephritis and the diseased kidneys removed Thus it is clearly established that, in the maintenance of chronic renal hypertension, no irreversible extrarenal mechanism—structural or neurogenic—supervenes This does not of course exclude the participation of some extrarenal factor, but it does indicate that in this form of chronic hypertension a metabolic renal disturbance almost certainly plays a primary role in resetting the homœostatic regulation of the blood-pressure at a higher level In other forms of chronic hypertension, including essential hypertension, this line of reasoning is effectively blocked by the fact that, at any rate until the late stages, there is no structural basis for a renal mechanism If therefore the kidney plays a role in the pathogenesis of essential hypertension it must be on the basis of a purely functional disorder, or of structural changes which have not been so far revealed by light microscopy This is a main problem for future investigation One of the most urgent needs is a further clarification of the mechanism of renal hypertension, for, from what has been said, this may open the way to an understanding of other forms of chronic high blood-pressure

Views on the pathogenesis of essential hypertension have recently been expressed, on this and other occasions, in which the high blood-pressure is deemed to depend on a variety of influences—genetic, nervous, emotional, dietary, renal, and endocrine—with the corollary that no specific cause is likely to be found in the great majority of cases These " multiple choice " hypotheses, which embrace all the possible mechanisms of blood-pressure variation, fail to distinguish, and indeed seem to discount the need to distinguish, these mechanisms from their provoking causes The modes of production of blood-pressure elevation are undoubtedly manifold and may differ in the wide variety of individuals who present with arterial hypertension But some single factor or limited combination of specific factors may well determine that one person gets " essential hypertension " whilst another does not

Conclusion

From these far-ranging discussions I have attempted to outline recent trends in various lines of research which seem to offer promise for the future The Prague symposium made a valuable contribution by bringing together workers from East and West, and by providing the fullest opportunities for critical discussion of their diverse views It brought to the fore the problems and possibilities of epidemiological research on the subject, and presented fresh evidence and ideas on hæmodynamic factors Perhaps of greatest importance was the large representation from the basic sciences—chemistry, physics, physiology, and pharmacology—for from these disciplines are most likely to come new techniques and methods of inquiry

The programme arrangements of the symposium placed the emphasis on discussion rather than presentation of papers, and this was something of an experiment on which both W H O and the Czechoslovak Cardiological Society are to be congratulated What cannot be omitted is a sincere appreciation of the work and friendliness of our medical colleagues in Prague, whose hospitality was not only generous but very largely personal and spontaneous

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THE FUTURE OF GENERAL PRACTICE

The future of general practice was considered by Dr Oscar Williams in a presidential address to the Association of Welsh Executive Councils at Llandudno on Oct 28

Dr Williams remarked that it had been said that the general practitioner was dead It was certainly true that, except in residential suburbs and south-coast resorts, applications for practice vacancies had fallen almost catastrophically What was to be done ?

The clock could not be put back no practitioner could now, as he did formerly, cope with all emergencies and problems But the pendulum had swung too far the other way, for today the practitioner was forced to refer a high proportion of his patients to a specialist or a succession of specialists before initiating treatment, and sometimes he might lose all control over his patient's treatment

Inevitably the status of the practitioner (he could now hardly be called family doctor) had suffered—and this at a time when in the higher administrative places opinion was moving away from increased institutional treatment, particularly of mental illness, of the very young and very old, and even for midwifery

Those who served on executive councils should welcome this rethinking, and should determine forthwith to play a more creative part in building a complete domiciliary service—an aim which could be achieved only in cooperation with the public-health, hospital, and social services The general practitioner could then become more of a personal doctor, concerned with the social aspects of disease, able and willing to advise the family on its problems, the children, the aged dependants, and the difficulties when the family had to cope with a mentally ill member

Unfortunately there was at present little incentive to this end The Royal Commission on the Remuneration of

Doctors and Dentists had not supplied the answers its report implied that indifferent work paid. The essential minimum requirements were as follows.

The practitioner should have more time to devote to each patient, and this entailed at once cutting big lists and lowering maxima.

He should be properly housed, with all the ancillary help he needed.

He should work closely with his hospital and other colleagues, and he should in fact be invited to participate actively in the work of the hospital and of local-authority clinics, thus averting the frustrations of overlapping.

He should be allowed far more practical participation in the work of hospitals. Clinical assistantships limited to six months' tenure were not the answer, nor even was the provision wherever possible of general-practitioner beds. A family doctor should be able to graduate into the hospital service, as he could formerly.

Another difficulty, which had been only half faced, was the general practitioner's security, or lack of it. The doctor should have the right, without fear of losing his patient, of advising the patient firmly on the course he should pursue, and not merely prescribe the latest tablet. A change of doctors should not be allowed without adequate grounds. Finally, there should be some recognition of higher standards of work.

PENSION AND BENEFIT INCREASES

The proposed increases in pensions, benefits, and contributions, foreshadowed in the Queen's speech, were announced by Mr John Boyd-Carpenter, Minister of Pensions and National Insurance, on Nov 2. The increases, which will cost an extra £160 million a year, will, subject to parliamentary approval, begin next April.

War Pensions

The basic rate of pension for 100% war disablement will be raised by 12*s* 6*d* a week to 97*s* 6*d*. Pensions for war widows with children, or over forty years of age, will be increased by 10*s* a week to 76*s*, with further increases for their children.

National Insurance Benefits

The standard rates of retirement and widows' pensions and sickness and unemployment benefits will go up to 57*s* 6*d* a week for single people and to 92*s* 6*d* a week for married couples, increases of 7*s* 6*d* and 12*s* 6*d* respectively. The allowance for each dependent child will be increased by 2*s* 6*d* a week, and for a widow's child by 5*s*. Maternity benefits, the guardian's allowance, and the child's special allowance are also being raised.

Industrial Injuries Benefits

Injury benefit, now 85*s* a week, will be increased to 97*s* 6*d* a week as will the pension for 100% disablement. The industrial widow's pension of 56*s* a week will go up to 64*s*.

Contributions

The flat-rate contributions for employees in the graduated scheme will stay at about their present level instead of being reduced from next April. The flat-rate contributions for employees contracted out of the graduated scheme, for the self-employed, and for the non-employed will be increased. The contribution from the taxpayer will also be increased.

National Assistance

The scale rates for National Assistance will be raised by 3*s* 6*d* a week for a single householder and by 5*s* for a married couple, to 53*s* 6*d*. and 90*s* respectively. There will be suitable increases in the other rates, including those for dependants.

Symposium

IMMUNOLOGY IN THE RHEUMATIC DISEASES

The Empire Rheumatism Council held a symposium on Immunology in the Rheumatic Diseases in London on Oct 28, under the joint chairmanship of Dr W S C Copeman and Prof John Squire.

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Reporting a joint study with Dr I M Roitt, Dr W Hijmans (Leiden), and Dr E J Holborow, Dr Deborah Doniach (London) described results of testing sera from patients with thyroiditis, systemic lupus erythematosus (S.L.E.), and rheumatoid arthritis for the presence of antibodies to thyroid antigens, antinuclear factors, anticytoplasmic factors, and rheumatoid factors. About 10% of Hashimoto patients gave positive antinuclear or anticytoplasmic tests, and the incidence of low-titre anti-thyroglobulin antibodies was increased in S.L.E. patients.

Serum complement was diminished in S.L.E., Dr H A. Ellis (Birmingham) found, and might be increased in early active rheumatoid disease, although it fell later, especially when rheumatoid-factor titres were high.

Dr R. R. A Coombs (Cambridge) described the factor—immunoconglutinin—which appears in the serum of rabbits immunised with bacteria specifically agglutinated with antibody in the presence of complement, or indeed immunised with bacteria alone. This factor, apparently an auto-antibody to complement, can be detected in the serum in many human infections, but is increased also in rheumatoid arthritis.

Dr R. G White (London) described the use of immunofluorescent methods to locate -globulin intracellularly in the plasma-cell series in the medullary tissue of lymph-nodes, and in their germinal centres. He drew attention to the follicular hyperplasia and plasma-cell proliferation found in rheumatoid lymph-nodes.

The significance of the rheumatoid serum factors was discussed by Dr J Ball (Manchester), who said that the rheumatoid macroglobulin factor for rabbit globulin could be detected in about 40% of adults, and in significant titre in 2–5% of Northern Europeans. Positive tests were found (apart from rheumatoid arthritis) in a significant proportion of cases of S.L.E., systemic sclerosis, digital arteritis, and Sjogren's syndrome. About 35% of positive tests in a random sample were associated with clinically detectable disease.

Dr C L Greenbury (Stoke Mandeville) described quantitative experiments using radio-iodine to label rheumatoid factor or antibody, which indicated that the amount of factor removable by repeated absorption from a given serum varied according to the degree of sensitisation of the absorbing red cells.

Dr B Cruickshank (Glasgow) doubted whether -globulin was significant in the ætiology of rheumatoid disease. Only a minority of the plasma-cells in the inflammatory lesions of rheumatoid tissue had been shown to contain either 7S or 19S -globulin. He had found histological changes in synovial tissue in ankylosing spondylitis essentially similar to those in rheumatoid arthritis, but associated neither with serum and experimental observations, which is certainly relevant to the problem of chronic hypertension in general, and possibly by analogy to essential hypertension This is the growing evidence of a change in mechanism when high blood-pressure passes from the acute to the chronic stage Thus when hypertension is caused by some specific lesion—e g , phæochromocytoma, adrenal cortical tumour or unilateral renal disease—the pressure frequently remains elevated when the primary cause is removed As far as present evidence goes, it does not seem possible to distinguish this chronic residual hypertension from essential hypertension on clinical, physiological, or anatomical grounds There is some evidence also of a difference in mechanism between the hypertension of acute and chronic nephritis and early and late experimental renal hypertension These observations underline the importance, first, of looking for a similar change in mechanism in the development of essential hypertension, and, second, of considering the possibility of a common factor in the various forms of chronic high blood-pressure The striking thing is that in all these conditions a new equilibrium appears to have been established at a high level of blood-pressure which is consistent with many years of good health This would appear to involve a “ resetting ” of the homœostatic mechanisms which normally maintain arterial pressure at a steady level There is evidence of such a resetting in the case of the baroceptors, but, as already mentioned, the evidence does not suggest that this is of causal significance One of the most clear-cut observations in this field is the reversibility of chronic renal hypertension In the laboratory animal, renal hypertension of long duration is reversed within a matter of hours if the renal circulation is restored to normal In man a similar prompt reversal of chronic renal hypertension has been demonstrated when, in identical twins, a normal kidney has been grafted in a twin with chronic nephritis and the diseased kidneys removed Thus it is clearly established that, in the maintenance of chronic renal hypertension, no irreversible extrarenal mechanism—structural or neurogenic—supervenes This does not of course exclude the participation of some extrarenal factor, but it does indicate that in this form of chronic hypertension a metabolic renal disturbance almost certainly plays a primary role in resetting the homœostatic regulation of the blood-pressure at a higher level In other forms of chronic hypertension, including essential hypertension, this line of reasoning is effectively blocked by the fact that, at any rate until the late stages, there is no structural basis for a renal mechanism If therefore the kidney plays a role in the pathogenesis of essential hypertension it must be on the basis of a purely functional disorder, or of structural changes which have not been so far revealed by light microscopy This is a main problem for future investigation One of the most urgent needs is a further clarification of the mechanism of renal hypertension, for, from what has been said, this may open the way *to an understanding of other forms of chronic high* blood-pressure

Views on the pathogenesis of essential hypertension have recently been expressed, on this and other occasions, in which the high blood-pressure is deemed to depend on a variety of influences—genetic, nervous, emotional, dietary, renal, and endocrine—with the corollary that no cause is likely to be found in the great majority s These “ multiple choice ” hypotheses, which race all the possible mechanisms of blood-pressure variation, fail to distinguish, and indeed seem to discount the need to distinguish, these mechanisms from their provoking causes The modes of production of blood-pressure elevation are undoubtedly manifold and may differ in the wide variety of individuals who present with arterial hypertension But some single factor or limited combination of specific factors may well determine that one person gets “ essential hypertension ” whilst another does not

Conclusion

From these far-ranging discussions I have attempted to outline recent trends in various lines of research which seem to offer promise for the future The Prague symposium made a valuable contribution by bringing together workers from East and West, and by providing the fullest opportunities for critical discussion of their diverse views It brought to the fore the problems and possibilities of epidemiological research on the subject, and presented fresh evidence and ideas on hæmodynamic factors Perhaps of greatest importance was the large representation from the basic sciences—chemistry, physics, physiology, and pharmacology—for from these disciplines are most likely to come new techniques and methods of inquiry

The programme arrangements of the symposium placed the emphasis on discussion rather than presentation of papers, and this was something of an experiment on which both W H O and the Czechoslovak Cardiological Society are to be congratulated What cannot be omitted is a sincere appreciation of the work and friendliness of our medical colleagues in Prague, whose hospitality was not only generous but very largely personal and spontaneous

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THE FUTURE OF GENERAL PRACTICE

THE future of general practice was considered by Dr OSCAR WILLIAMS in a presidential address to the Association of Welsh Executive Councils at Llandudno on Oct 28

Dr Williams remarked that it had been said that the general practitioner was dead It was certainly true that, except in residential suburbs and south-coast resorts, applications for practice vacancies had fallen almost catastrophically What was to be done?

The clock could not be put back no practitioner could now, as he did formerly, cope with all emergencies and problems But the pendulum had swung too far the other way, for today the practitioner was forced to refer a high proportion of his patients to a specialist or a succession of specialists before initiating treatment, and sometimes he might lose all control over his patient's treatment

Inevitably the status of the practitioner (he could now hardly be called family doctor) had suffered—and this at a time when in the higher administrative places opinion was moving away from increased institutional treatment, particularly of mental illness, of the very young and very old, and even for midwifery

Those who served on executive councils should welcome this rethinking, and should determine forthwith to play a more creative part in building a complete domiciliary service—an aim which could be achieved only in cooperation with the public-health, hospital, and social services The general practitioner could then become more of a personal doctor, concerned with the social aspects of disease, able and willing to advise the family on its problems, the children, the aged dependants, and the difficulties when the family had to cope with a mentally ill member

Unfortunately there was at present little incentive to this end The Royal Commission on the Remuneration of

Doctors and Dentists had not supplied the answers its report implied that indifferent work paid The essential minimum requirements were as follows

The practitioner should have more time to devote to each patient, and this entailed at once cutting big lists and lowering maxima

He should be properly housed, with all the ancillary help he needed

He should work closely with his hospital and other colleagues, and he should in fact be invited to participate actively in the work of the hospital and of local-authority clinics, thus averting the frustrations of overlapping

He should be allowed far more practical participation in the work of hospitals Clinical assistantships limited to six months' tenure were not the answer, nor even was the provision wherever possible of general-practitioner beds A family doctor should be able to graduate into the hospital service, as he could formerly

Another difficulty, which had been only half faced, was the general practitioner's security, or lack of it The doctor should have the right, without fear of losing his patient, of advising the patient firmly on the course he should pursue, and not merely prescribe the latest tablet A change of doctors should not be allowed without adequate grounds Finally, there should be some recognition of higher standards of work

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PENSION AND BENEFIT INCREASES

THE proposed increases in pensions, benefits, and contributions, foreshadowed in the Queen's speech, were announced by Mr John Boyd-Carpenter, Minister of Pensions and National Insurance, on Nov 2 The increases, which will cost an extra £160 million a year, will, subject to parliamentary approval, begin next April

War Pensions

The basic rate of pension for 100% war disablement will be raised by 12*s* 6*d* a week to 97*s* 6*d* Pensions for war widows with children, or over forty years of age, will be increased by 10*s* a week to 76*s*, with further increases for their children

National Insurance Benefits

The standard rates of retirement and widows pensions and sickness and unemployment benefits will go up to 57*s* 6*d* a week for single people and to 92*s* 6*d* a week for married couples, increases of 7*s* 6*d* and 12*s* 6*d* respectively The allowance for each dependent child will be increased by 2*s* 6*d* a week, and for a widow s child by 5*s* Maternity benefits, the guardian s allowance, and the child's special allowance are also being raised

Industrial Injuries Benefits

Injury benefit, now 85*s* a week, will be increased to 97*s* 6*d* a week, as will the pension for 100% disablement The industrial widow's pension of 56*s* a week will go up to 64*s*

Contributions

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Dr J N **McCormick** (Stoke Mandeville) had used partially denatured human γ-globulin labelled with fluorescein to detect rheumatoid factor in unfixed frozen biopsy material from rheumatoid arthritis The cells containing the factor were mainly plasma-cells, and were most numerous in rheumatoid synovial tissue The globulin of the germinal centres, although abundant, appeared to contain very little rheumatoid factor

Fluorescence methods of locating tissue antigens (using fluorescein and rhodamine conjugates) were also described by Dr G **Scott** (Stoke Mandeville) Using anti-glomerulus and antisynovial-membrane conjugates, he had defined three components of human connective tissue by immunohistochemical staining

Dr W R M **Alexander** (Edinburgh) had found that synovial fluid from rheumatoid-arthritis patients injected intradermally in other patients or controls, often gave rise to a delayed skin reaction, apparently of the Mantoux type The active factor, a γ-globulin, was very unstable, and usually did not cause a reaction in the donor's own skin

Discussing his experience with antinuclear serum factor as revealed by the fluorescent-antibody method, Dr D M **Weir** (Taplow) said that the factor was almost invariably present in S L E, but was also found in rheumatoid arthritis, discoid lupus, and some other related conditions, although much less frequently and usually in lower titre He described laboratory investigations on the nature of the antigen(s) reacting with the serum factor

Dr G J **Friou** (Yale) had studied antinuclear factor using fluorescent and radioactive labelled antihuman globulin with whole nuclei, and nucleoprotein, as antigens

Dr W **Hijmans** (Leiden) regarded the L E cell factor as an antibody against nuclear material, and described quantitative precipitin studies between desoxyribosenucleic acid and serum, and complement-fixation studies with histone He gave reasons for not considering the serum factor as pathogenic

Dr E J **Holborow** (Taplow) considered the antigenic possibilities of the polysaccharides of connective tissue He outlined natural and experimental methods of enhancing antigenicity of polysaccharides and drew attention to the lack of knowledge of whether they could take part in hypersensitivity reactions

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Medicine and the Law

The New Criminal Justice Bill

This Bill deals mainly with offenders under 21 Its main objects are to make wider provision for the use of borstal training and of detention centres in dealing with young offenders, to discontinue short sentences of imprisonment as more detention centres become available, and to extend the provision of compulsory aftercare Changes are also proposed in the law relating to approved schools

Part I remodels the custodial forms of treatment for young offenders No new forms of treatment are proposed, but existing methods, particularly borstal training and detention centres, are extended to more offenders Imprisonment will eventually be restricted to cases where no other sentence is appropriate The new scheme depends on the provision of more borstals and more detention centres, and will be introduced by stages as the additional institutions are ready

Borstal Training

The minimum age for a sentence of borstal training is lowered from 16 to 15 and the court will be able to pass such a sentence whenever they think it expedient that the offender should be detained for training for not less than six months But if an offender is under 17, the court, before passing a borstal sentence, must decide that no other method of dealing with him is appropriate The maximum term of borstal training is reduced from three years to two years and the minimum term from nine months to six months

Imprisonment

The imprisonment of young offenders is restricted to sentences of not more than six months or long sentences of three years or more (except for some offenders who have already been in prison or a borstal) Short sentences of imprisonment are to be abolished by stages as more detention centres become available Imprisonment of offenders under 17 is abolished, but the power of the higher courts to sentence children and young persons found guilty of grave crimes to detention as the Secretary of State may direct is extended At present, this power is confined to offences of attempted murder, manslaughter, or wounding with intent to do grievous bodily harm The Bill extends it to include any offence for which an adult could receive a sentence of 14 years' imprisonment or more

Detention Centres

Where the court decides that a short period of training is appropriate, the offender will be committed to a detention centre For offenders until 17 dealt with by a magistrates' court, the period of detention will be a standard term of three months The higher courts will have discretion to fix the period of detention within a minimum of three months and a maximum of six

Approved Schools

The law about committal to an approved school is not altered, but the Bill provides that a boy or girl of not less than 15 can be removed temporarily from an approved school on a justice's warrant, if this is necessary to maintain discipline, to another approved school, a remand centre, or a remand home for up to twenty-eight days Offenders who turn out to be unsuitable for approved-school training, but are likely to benefit from borstal training may, with the consent of the Secretary of State, be brought before a magistrates' court, which will have power to order their transfer to borstal

Attendance Centres

The minimum age at which a child may be ordered to attend at an attendance centre is reduced from 12 years to 10

Fines

New and, in general, higher limits are set to the fines that magistrates' courts may impose in respect of offences committed by children and young persons, and the obligation on a parent to pay damages of costs awarded against his child is extended to the payment of compensation for loss Enforcement of fines will be by committal to a detention centre or a remand home for offenders under 17

Compulsory Aftercare

This is usually undertaken by probation officers It is extended for the first time to all offenders who are released from a detention centre (unless they were sent there for a default) and to some categories of people released from prison The extension of compulsory aftercare to ex-prisoners will be introduced by stages When it is completed it will include all sentences of four years or more whatever the age of the offender, all sentences of six months or more where the offender was under 26 at the start of the sentence, and all sentences of six months or more when the person has previously had a prison sentence of three months or more or a borstal sentence

In England Now

A Running Commentary by Peripatetic Correspondents

ONCE again the Director-General's Exercise—this year named White Swan—gave us a programme packed with interest, a shop-window of ideas for the future. Some will be discarded, but others will bear fruit I asked three very senior officers what was the biggest problem facing the Army Medical Services today One said the acquisition of broader professional experience. Another said the recruitment of other ranks (and gave me an entertaining lecturette on how to do it) The third said transport, transport, and transport again If you can transport the sick and wounded, quickly and shocklessly, over long distances to the medical centres, you can economise in medical manpower and equipment—and that appeals both to the operational commander, who wants to slim his administrative tail, and to the manpower planner, faced with a return to voluntary service after twenty years of conscription Transport today and tomorrow means air transport (the day after tomorrow it may mean hovercraft or rockets) and the D G duly showed us long-range aircraft, the rotodyne, helicopters—the lot. A French general told us about the enormous use made of helicopters by the French army in Algeria The six-year-old Algerian war has given the French more experience than any other nation of air evacuation, but he indicated that the French Army did not want to go on accumulating this experience.

We also saw the latest types of civil ambulance cars, some with bodies completely constructed of plastic reinforced with glass-fibre, which is strong, light, rustless, and never needs painting Yet with road congestion getting worse every day, will not the local health authorities have to invest in helicopters? Let the R.A.M.C. show the way At the Cambridge Hospital they could establish an accident centre, equipped with helicopters and aerial cameras, to serve the whole of the Aldershot district. The casualty department would be staffed with surgeons of the requisite experience, a helicopter-ambulance could be at the scene of an accident in a matter of minutes (even on bank holidays), and every accident could be photographed from the air What a contribution such a unit could make to research into the causation, prevention, and treatment of road accidents!

An excellent curry—made with dehydrated ingredients and served in a hangar—revived our spirits after the cold of the airfield. We saw the impressive efforts which are being made to modernise and improve military medical equipment The Plastic Age is dawning, and the reductions in total weight and bulk are nothing short of dramatic The new lightweight medical panniers were demonstrated by an extremely smart Nigerian private who has won the Duke of Edinburgh's gold award

I am not yet convinced of the value of the universal container—a lightweight room that can be carried by air and deposited on any little flat piece of ground We saw it being used as an operating-theatre, as a pathology laboratory, as an advanced medical store, as a heatstroke centre, and as the examination and treatment room for a 10-bed medical reception station Perhaps it was the sight of ten "patients" lying in bed in the pouring rain (were there not enough canvas roofs to go round?) that made me feel that further experiment in the design of tentage and supports is what is really needed. The School of Health gave us an admirably straightforward demonstration of ten basic health routines for the soldier, after which there was a bit of a barney about urine tests for paludrine.

The Exercise gets more like an international congress every year None of the American officers would hazard a guess on the result of the Presidential election Eminent officers from the Indian subcontinent spoke to me gloomily about the changed status of their 2000-year-old Maginot Line of the Himalayas A Canadian officer told me that the integration of the Canadian Forces medical branches (which so bewitched our political mentors in the Select Committee on Estimates) had scarcely changed anything Just at present, integration seems to be more urgently needed in certain political circles than anywhere else. At the Exercise supper a well-known authority on malaria prevention presided with patriarchal dignity over a table of pretty nursing officers, and somebody round the piano sang "I'm Dreaming of a White Swansong"

* * *

I am, I confess, a secret thinker, and one day in the rush-hour I caught myself at it again. Suppose a Neptunian scientist (people on Neptune are very large) knowing nothing about life on Earth were to hover over some of our greater cities, studying the traffic. He would notice that the multicoloured shining particles which moved in certain natural channels appeared to obey certain laws These laws, it is true, would not always be rigidly followed, they would be approximate, statistical, stochastic laws, similar to those of chemical kinetics and thermodynamics in our own scientific culture. He would observe, for example, that when a space appeared among a stream of particles, one of them would inevitably sooner or later move into the gap, so that the place left behind it could in turn be filled by another particle and so on, giving the overall effect of a sluggish wave-like forward motion. He might well postulate some kind of force, tending to move the particles by mutual pressure into regions of low population density "Nature", he might aphoristically say to himself, "abhors a vacuum." Or he might notice that when the population-density was high, the noise-level also tended to be high, or there might be a relation between the average rate of the forward wave-motion and the density, or between the noise-level and the mean distance travelled without collision. In short, our Neptunian might soon build up a set of traffic laws akin to the gas laws of physics

At this point in my meditations I stopped my forward wave-motion with something of a jolt, causing a transient sharp rise in the local noise-level. If a Neptunian were to look on us like that, would he be doing anything fundamentally different from what we do when we study the molecules of a gas? And would it ever occur to him that each one of those curious shiny particles, with their semi-random, semi-determinate motions, might contain a living, sentient, meditative being such as myself? Well, then, how about the gas molecules? Who might there not be inside them, I asked myself And, do you know, the thought has bothered me since After all, how do we know that an atom doesn't think of itself as ME? It's time somebody looked into the matter, in my opinion, because if we go on treating the atoms the way we do now, some day there'll be trouble.

* * *

We had a rotten trip back fom the States Even the official log of the *Mauretania* described the conditions as "strong N'ly gale, very rough sea, very heavy N'ly swell" After long deferment of hope in successive arrivals at Cobh and Le Havre, we reached Southampton I telephoned my wife and arranged for her to meet me in Newcastle at 7 A.M The boat train took me to London, where I boarded the sleeper at King's Cross

I woke up at 6 A.M., and reflected that this was the ninth day since leaving New York, but that I would be home in an hour The attendant brought tea I remarked that it seemed very quiet outside. "Yes, Sir," he said, "I'm afraid we're still in Northallerton, and we're an hour behind time. I'm just going to find out what's the matter" He was back in a few minutes to say "It seems, Sir, that the fire went out. They're busy trying to get it going again."

Not even the rich new expletives that I had learnt in America were of any use to me I was speechless

* * *

Our quiet, shy, third-year medical student disappeared behind the screens to examine a middle-aged blonde patient All was well for a few minutes as his examination proceeded, but suddenly the quiet of the ward was shattered by scream upon scream and the words "I wouldn't even let my husband do that." The student emerged blushing furiously to explain to

Sister, who advanced in a menacing way, that he had only been eliciting the patient's plantar responses

* * *

A long time ago I made the mistake of learning how to use a desk calculating machine It was useful to me at the time, because I do not like doing sums and it was much nicer to have a thing like a typewriter to do them for me But it got me a reputation which did me no good at all, and I became known as the department's statistician (unpaid and quite extra to my proper jobs) and general calculator-man I have never been strongminded enough either to repudiate the status or to insist on people learning to do sums for themselves Now, to put the seal on my position, I have been sent on a computer course because " it might be useful if you get the know-how "

I must say the computer people were very nice and friendly to us (I could be friendly too, if someone wanted to learn from me how to use my little desk machine instead of wanting it done for him) Their machine was friendly too, a bit dour the first time we called on him, but then he was said to have a pain in his inside, and an appreciable smell of beer in his neighbourhood suggested that he knew how to look after himself when out of sorts Later he was in splendid form, inverting a large matrix and playing a happy tune on his hooter to announce progress after each thousandth sum or so—i e , a brisk toodleoodleoo, with a thousand to each " ooo " Our job, it appeared, was to learn a language which he could understand well enough to translate into his own dialect, and presently we were writing

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A = 2
B = 2
A = AB
PRINT (A)
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which seemed a funny way of putting 2 × 2 and downright wrong algebra But presently we grasped bits of it, and were happily composing letters to the supermachine and even typing them ourselves on the teleprinter which makes the only kind of signs he is really interested in reading

By the end of the course the real mathematicians had become obvious, while some amateurs had fallen by the wayside altogether This was not quite my fate, but I did get a bit mixed up about what was computer-work and what was not I wandered into the unit's common room and was interested to find *The Times* with the crossword only half done The supermachine couldn't have been too slow to finish, it was nice to think that in some ways he might have been too stupid But then computers are apt to have a streak of stupidity look at me still doing the department's sums for them I never thought that this course would show me that what I have most in common with supermachines is a willing nature

* * *

Aunt Pash must be one of my oldest patients She is said to be 93, has one eye, and a colostomy She lost her eye in " one of they girlish pranks " I am not sure what she means by that, but knowing Aunt Pash, I fear the worst I usually visit her hut on the beach when I am in that part of the district, but three times lately it has been empty, and neighbours told me that Pash was visiting However, the last time I was up the Bay, she was home again, and her hut was, as ever, chaotic with spinning and quilting This time there were no tales of her girlhood—the more lurid of which always ended with 'Ah, my dear, the tales I could tell'ee, the tales I could tell ee " No, she had been out gallivanting, and mightily she had enjoyed herself A distant cousin had moved house, and she had gone to help Now it may not be remarkable for an elderly lady to hold very small pieces of china at a housemoving, but in Newfoundland housemoving literally means housemoving The house is taken from its foundation, hauled down to the edge of the water, floated on to a raft, and towed to its new site Once there it is dragged out and hauled into position It is a backbreaking job, and all hands are needed on the lines This is what Aunt Pash had been doing on her holiday Later I was told that she had worked as hard as anyone and cussed better than most I don t doubt it at all

Letters to the Editor

FUTURE ORGANISATION OF PATHOLOGISTS

SIR,—Since with the approach of voting-day for pathologists, past-presidents of the Association of Clinical Pathologists have written to press the advantages of the recent " offer " of the Royal College of Physicians, I write to point to one important fact and event in the history of the Association that has been omitted from recent discussion and documents

The Association of Clinical Pathologists became incorporated on Feb 12, 1956 This was the culmination of the labours of a devoted secretary and had been pursued with enthusiasm by presidents, officers, and council, and the members and all knew that this was the initial stage in the formation of a new and independent college

What is it, therefore, that has caused presidents, officers, and council now so eagerly to favour " the present generous and unequivocal terms " of the recent offer of the Royal College of Physicians ?

That a diploma of membership of a division or faculty of a Royal college would be an almost immediate result of acceptance of the offer is certain, and this would meet one of the needs of pathologists without any great effort—merely the subscription of foundation membership, or examination and membership fees But the status that this diploma might confer would be somewhat reduced by the inferiority attaching to a division or faculty (That a faculty is regarded as inferior is witnessed by the current action of a most ancient medical faculty that seeks by legislation to alter its title to Royal College of Physicians and Surgeons of Glasgow) Surely, the seniors in the Association are not unaware of this implication of inferiority which is not disguised by the use of the term division Why is it therefore that they advise a " short-cut " when the Association has progressed to incorporation unaided ? Everyone knows that a new and independent college may require a few years to have its diploma of membership recognised, everyone knows that a new college is not founded and nurtured without great effort and equally great sacrifice Those who earnestly and sincerely consider that an independent college should be the heritage of our registrars, and in turn their registrars, would work willingly and make sacrifices Is it that in the remaining years of their working lifetime the seniors would rather they held high office and examinership in a subsidiary faculty (of which they are fellows through being fellows of the parent college) than be concerned with great efforts the fruits of which would be enjoyed by posterity and not by themselves ? Or, to put it at a higher level, is it that the senior pathologists who are fellows of the Royal College of Physicians are using their influence to secure to this college, at the time of rebuilding, and for a long time, revenue from the pathologists that in the first instance might amount to around £25,000 ?

London, N 18 J F HEGGIE

SIR,—Dr Joan Taylor and Professor Pulvertaft are two of my oldest friends, but I am bound to tell them that most of their letter of Nov 5 is rubbish

Professor Pulvertaft has had much experience in the appointment of pathologists Has he ever found the absence of a specific higher qualification a handicap ? And if so, how often ? (In this debate a few quantitative statements will be refreshing) He makes appointments, as everyone else does, on the confidential advice of his colleagues and on his own judgment If he has made an occasional mistake I have little doubt that it has been when the flutterings of his warm heart have silenced the warnings of his cool head In our lifetime it has been characteristic of pathology—more, I think, than of any other branch of medicine—that it has drawn its adepts from a wide variety of sources the preclinical sciences, public health, and general practice have all contributed colleagues whom we respect There have been those pathologists who combined the humblest medical qualifications with fellowship of the Royal Society It is one of the weaknesses of the N H S that it is more difficult than it was to change from one specialised branch to another To add any degree or diploma which makes the entry into pathology more difficult or more rigid can only impoverish the science

"Academic centre" is, I suppose, looking-glass language for a college or faculty The adjective is an unusual one to apply to any existing body of this kind except, perhaps, the Royal College of Surgeons As for "a body to speak for pathologists", things have come to a pretty pass if Dr Taylor and Professor Pulvertaft are no longer able to speak for themselves To whom is this body to speak and about what? And who on earth would be able to speak for such a disorderly mob of individualists as we are?

In all this interminable debate the talk has always been of examinations and diplomas but seldom of training Is it not time that we abandoned this babu attitude? The Doctor and the Professor and I all learned pathology in the bad old way, picking up knowledge and experience as we could, piecemeal and without a plan The example of the course for the diploma in bacteriology has shown that a more systematic training is not only possible but desirable I see no reason why the same methods should not be applied to other branches of pathology if some university will give them a trial

Hoccombe, Somerset J A BOYCOTT

SIR,—For Dr Joan Taylor and Professor Pulvertaft I have the greatest admiration and respect, but their idea of an academic centre for pathology in London seems completely out of touch with the ideas of those of us who work some distance from London

The higher qualification and the body to speak for pathologists can be achieved at a very small cost Dr O'Gorman (Nov 5) is rightly daunted by the cost of a building, but what pathologist outside London is going to use such a building?

For meetings, the Pathological Society and the Association of Clinical Pathologists have been able to enjoy the hospitality of numerous bodies all over the country The College of Pathologists could do likewise

Why should not the College of Pathologists start in a small way like the Royal College of Obstetricians and Gynæcologists?

As for withdrawing, as Dr O'Gorman suggests once we are in the Royal College of Physicians it will be impossible to withdraw from that body without its permission The constitution of that body is authoritarian, and it would be unreasonable to expect permission to withdraw to be granted, as G G implies (Nov 5, p 1025)

No, Sir! The only solution appears to be the logical conclusion of Peter Davey's argument He says that the physicians are notable Greek scholars They therefore know that a pathologist is a man who studies disease Their work is therefore pathology, not physic, which is the study of Nature

Let them show their greatness by changing their name to the Royal College of Pathologists We will then join in with them, so possibly will the other Royal Colleges! (Or am I optimistic?) We shall then have a body able to speak for the whole of Medicine

The alternative more likely to be acceptable is for the pathologists to have their own College, and for all the medical colleges, faculties, associations, and societies to join together to form an Academy of Medicine for that purpose

Mumbles, Swansea H C M WALTON

SIR,—As an ordinary pathologist of a very peripheral hospital, may I support the plea of Dr Joan Taylor and Professor Pulvertaft for a vote in favour of the division of pathology within the Royal College of Physicians I started this year firmly in favour of an independent college and, because of the accident that it was my turn to be branch president, found myself defending this view on behalf of the North of England branch at a special meeting of the council of the Association of Clinical Pathologists held in February Because of this I subsequently had quite a long exchange of views with various members of the council, and have since become convinced that a division within the Royal College of Physicians will meet our needs

In the Widdicombe File, G G discusses the various obstacles in the way of an independent college and shows how they might be overcome, but he does not mention the greatest obstacle of all This is that the great majority of the leaders of our specialty do not favour the establishment of an independent college at the present time, but, in all sincerity, prefer the R C P solution It seems to me that it is possible and right for the main body politic of the Association of Clinical Pathologists to stop—if it so wishes—its leaders from going a certain way, but more than this is not possible The real issue in the forthcoming poll therefore is not between the R C P and an independent college but between the R C P and nothing at all for many years to come With the Royal Commission finished, the next ten years may be all-important in shaping the future pattern of British medicine, and it will be bad for both medicine and ourselves if during this time we alone among the major specialties have no official organisation

Northallerton P N COLEMAN

SIR,—Discussions on the future of clinical pathology have assumed that it has a future in the form we know today The supporters of a College of Clinical Pathologists ought to discuss this assumption and have not done so, association with the Royal College of Physicians involves considerably less mortgage of the future

We are not endowed with the gift of prophecy Twenty-five years ago few would have envisaged the position that clinical pathology enjoys today To assume that the present pattern will exist unchanged in 1985 is to make an improbable assumption Two branches (hæmatology and chemical pathology) are growing rapidly and show signs of passing out of the ken both of the general physician and of the clinical pathologist Hæmatology is already well on the way to becoming a subspecialty of internal medicine More slowly, chemical pathology is going the same way, the advent of automation, lessening as it must preoccupation with technique, will accentuate this trend Of the other branches of clinical pathology, hospital bacteriology is being divided more and more between the specialists in hygiene and therapeutics Remains pathology proper, the practitioners of which have always had a well-defined subject which does not take them to the bedside nor make them primarily technicians, it is probably the branch of pathology destined to change the least It seems at least unlikely that most of the subject-matters of clinical pathology will remain in the hands of a group called clinical pathologists and a College of Clinical Pathologists, if established, could become another South Sea House and an obstacle to progress

For reasons set out by Dr Joan Taylor and Professor Pulvertaft present action is needed such action should leave the future uncommitted as far as possible Association with the Royal College of Physicians is the only logical course

Sheffield ARTHUR JORDAN

*** A letter from the Widdicombe File appears on p 1094 —ED L

USE OF BRL 1241

SIR,—Dr Novick's letter (Oct 29) covers well-trodden ground and adds little except speculation to what we already know By now several thousand strains of *Staphylococcus pyogenes* have been tested, and so far no "celbeninase"-producing organisms have been found This suggests that they are rare if they exist at all, and are considerably rarer than penicillinase-producers were at the time of the introduction of penicillin On the other hand we are all agreed that bacteria often yield mutants which bypass the injurious effects of a chemical agent in some way other than destroying the drug This is an alternative and more common method of developing resistance to an antibiotic In the case of penicillin such mutants can readily be obtained by selection in the laboratory, but have not been shown to be the cause of lesions in man Thus of the two kinds of resistance to penicillin only the one based on the destruction of the drug by an enzyme is clinically important Since 'Celbenin' is a derivative of penicillin having in all probability essentially the same mode of action it would be reasonable to expect that resistant mutants (non-"celbeninase") might also lack pathogenicity, even though retaining coagulase and other characters However, whether this expectation is unfounded, and strains *do* exist which retain sufficient virulence to be of clinical importance and in addition are endowed with sufficient communicability to occupy the biological space in hospitals, can be determined only by carefully controlled clinical observations

The demonstration of celbenin-resistant staphylococcal mutants was probable on general grounds and would be expected to follow the pattern of multiple steps of mutation seen with penicillin, each step resulting in greater resistance As the serum levels obtainable with celbenin at present are more restricted than with penicillin, it is conceivable that first or second step mutants could acquire sufficient resistance in vivo to escape therapeutic action, and yet retain pathogenicity With spraying, however, this is less likely to occur since much higher concentrations can be achieved locally and the mutants succumb to the higher doses of the drug Resistant mutants are not man-made, only selected, and on speculative ground at any rate are more likely to result from therapeutic use than from spraying

Dr Novick says that " it is conceivable that the method might be used indefinitely without unfortunate consequences, and it could be argued that the risk involved is acceptable in view of the advantages This risk must, however, be assessed in the light of the history of the fight against the staphylococcus " We submit that this is precisely what we did—bearing in mind the fundamental clinical problem of penicillin resistance

It must be admitted that a complete victory along these lines is perhaps not in sight, but that should not make one jettison a line of research on theoretical grounds The spraying of carbolic by Lister did not altogether banish hospital gangrene, but while it was in use undoubtedly saved a great number of lives We believe that the discovery of celbenin by the Beecham group was a milestone in the history of antimicrobial agents and will certainly lead to new and powerful drugs in the future In the meantime experiments with spraying should continue until their value is proved or their risk demonstrated on a factual basis

Bacteriology Department,
St George's Hospital
Medical School,
London, S W 1

S D ELEK
P C FLEMING

PROGNOSIS AND ANTICOAGULANT PROPHYLAXIS AFTER CORONARY OCCLUSION

SIR,—In their very valuable article of Nov 5 Professor McMichael and Dr Parry suggest that the unusually good 5-year survival-rate of doctors after cardiac infarction is because "no doubt they can take greater care of themselves and avoid undue physical strain" It is surprising that the authors, who are so rightly critical of loose thinking and imprecision in others, should make such a dubious statement What does "taking care of themselves" mean? And what evidence is there that "avoiding undue physical strain" prevents further infarcts?

I submit that a more plausible explanation of the apparent good prognosis in doctors is that their *minor* cardiac infarcts are more often diagnosed than are the minor infarcts of the laity, the symptoms of which are apt to be attributed to "indigestion"

Farnham, Surrey JOHN W TODD

POSTPARTUM PRE-ECLAMPSIA

SIR,—I have read Flight-Lieutenant McFadyen's article of Nov 5 and should like to make the following comments

I have already shown[1–4] that the contracting postpartum uterus provokes renal ischæmia (which incidentally ergometrine might heighten, and this is evident in all the cases reported), that renal ischæmia is responsible for hypertension, œdema, and albuminuria, that hydramnios is an agent provocateur of renal ischæmia (main case), that pre-eclampsia is to be suspected with even minimal signs of the syndrome (main case), that there are many conditions that post partum can masquerade as pre-eclampsia (case 2 certainly being one in point) In fact his case-histories, if interpreted in the light of the data I have provided, amply support the thesis that the uterus resisting tension, which it does post partum also, provokes the uterorenal reflex from which the signs of toxæmia can all stem

Further I have collected sufficient evidence[5, 6] to show that the symptomatology of toxæmia is not comparable to Cushing's syndrome, that as toxæmia mounts so do the corticoids decline, that corticotrophin (A C T H) when given experimentally in human pregnancy does not provoke the syndrome, that eclampsia does occur when the adrenals have been previously extirpated, and that the placental production of corticoids is very small in contrast to that of the adrenals

May I also draw attention to two very important data?

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1 Sophian J Toxæmia of Pregnancy London 1953
2 Sophian, J *Excerpta Med* 1958 sec x, 2 no 1
3 Sophian J *Lancet* 1960 i 1351
4 Sophian J *Amer J Obstet Gynec* 1959 78 688
5 Sophian J *Lancet* 1958, i 434
6 Sophian J *Amer J Obstet Gynec* 1954 68, 733

Garrod [7] found that there was an immediate increase in glomerular filtration-rate (G F R) provoked by cortisone experimentally, while there is incontrovertible evidence to show that G F R is much decreased in toxæmia [1]

It would profit obstetricians to study the renal problem deeply To this end may I congratulate you on your enterprise in publishing an account (Sept 17) of the 1st International Congress of Nephrology at Evian, excellently compiled by Professor de Wardener

Worthing, Sussex JOHN SOPHIAN

CHEMOTHERAPY IN CHRONIC BRONCHITIS

SIR,—The paper by Dr Pridie and his colleagues (Oct 1) and the letter by Dr Aspin and Dr Howells (Oct 15) regarding long-term treatment of chronic bronchitis with antibiotics contain findings somewhat at variance with our own The minimum recommended dose of tetracycline or oxytetracycline for the continuous treatment of chronic bronchitis is 0 5 g daily, but we found 1 g per day to be the minimum satisfactory dose A smaller dose is in our view unlikely to be effective in the treatment of the majority of established cases of chronic bronchitis It does not seem to be a fair test of the efficacy of therapy to use a smaller and relatively ineffective dose With a dose of 1 g daily we have shown that the side-effects are much less significant to the patients than the incapacity which results from acute exacerbations of the disease in untreated cases

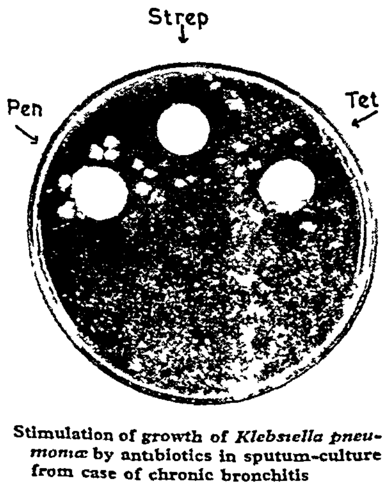
Further, the fullest bacteriological information can be obtained only by examining serial specimens of sputum freshly obtained from the patient We have shown that the correlation of the findings obtained from a single isolated specimen of sputum with the clinical state of the patients is poor The mere isolation of organisms not normally found in the respiratory tract, notably the coliform group, had little or no association with the clinical state of the patients, none of whom was treated in hospital

Departments of Infectious Diseases
and Bacteriology
City Hospital, Edinburgh

J McC MURDOCH
J C GOULD

SIR,—I note the letter by Dr Aspin and Dr Howells with particular interest because I have recently been associated with a clinical trial in chronic bronchitis to assess the value of vaccine therapy in contrast to the normal procedures of chemotherapy and antibiotic treatment

During this trial samples of sputum from some 50 patients were examined and we were particularly struck by the suppression of the normal flora with stimulation of growth of coliforms in vitro, using antibiotic-disc technique (see fig)



Stimulation of growth of *Klebsiella pneumoniæ* by antibiotics in sputum-culture from case of chronic bronchitis

This has led us to believe, as your correspondents suggest, that in treating chronic bronchitis intermittently with antibiotics the suppression of the usual flora may lead to consequent increased growth of the coliform organism

We have therefore persisted in our researches to determine what help vaccine therapy could give

We have been using a polyvalent oral vaccine for this purpose, and have had a great deal of assistance from general-practitioner colleagues in this project Should any of your readers be interested in helping us undertake a larger scale trial we should be grateful to hear from them and supply them with the necessary vaccine

Woodlands,
Windlesham, Surrey

R E DEREK LEIGH

SURGICAL REMOVAL OF BRANCHIAL SINUS

SIR,—I should like to congratulate Mr Allan Small on his article of Oct 22 Whether the condition is fistula or sinus is still a debatable point, but at The Hospital for Sick Children, Great Ormond Street, there have been many true fistulæ

This has been proved by the injection of dye into the track and its detection in the pharynx even before operation

The only point in the article that causes some concern is that related to thyroglossal cysts and their tracks I presume that Mr Small implies that the more difficult part of the dissection includes the excision of part of the hyoid bone and the very careful removal of the proximal part of the track as far as the foramen cæcum

If this point is not strongly stressed I am sure that the recurrence-rate in this condition will increase and lead to many more difficult secondary operations

The Hospital for Sick Children,
London, W C 1

S J COHEN

SIGNIFICANCE AND CLASSIFICATION OF FAT-EMBOLISM

SIR,—In his important paper of Oct 15 Dr Sevitt concludes that pulmonary fat-embolism produces no significant ill-effects in previously healthy subjects, and that it does not cause death even in those suffering from shock or blood-loss The validity or otherwise of this conclusion is of great practical importance, for it must influence the rationale of treatment If pulmonary fat-embolism is harmless then the thing to be avoided at all cost is systemic spread of the emboli, for there is general agreement that systemic fat-embolism is potentially a very serious condition Acting on this belief, some German workers [1–3] have practised a prophylactic regime whose object is the maintenance of “ controlled hypotension ”, in order to reduce the risk of pulmonary fat-emboli being forced through into the systemic circulation

I am less certain than Dr Sevitt that pulmonary fat-embolism is innocuous when very severe or when associated with shock or hæmorrhage The absence of a *characteristic* clinical symptom-complex does not necessarily mean that the condition is free from clinical manifestations of any sort It must be conceded that intravenous injection of fat in animals may produce severe effects and even death, although the lethal dose may be considered high there is a considerable species difference in tolerance—the dog, for example, is much more tolerant than the rabbit [4 5]—and results should not be applied uncritically to man Furthermore, there is abundant evidence that processes such as bleeding or the induction of tourniquet shock much reduce the tolerance of animals to intravenously injected fat [4–8] The contrary finding of Armin and Grant [9] stands alone and

may be attributable to the very small dosage which they employed

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[7] Garrod O, Davies, S H, Cahill, G J *J clin Invest* 1955, 34, 761

1 Fular, W, Kraft, E *Arch klin Chir* 1954 278, 548
2 Fular W Kraft, E *Medizinische* 1956 35 1197
3 Kronke, E *Arch klin Chir* 1956, 283 466
4 Harman J W Ragaz P J *Amer J Path* 1950 26 551
5 Halasz N A, Marasco J P *Surgery* 1957, 41, 921
6 Gold, E Loffler, E *Z ges exp Med* 1923 38, 153
7 Moser H Wurnig, P *Arch klin Chir* 1954, 278, 72
8 Whiteley, H W *J Path Bact* 1954 67, 521
9 Armin J, Grant, R T *Clin Sci* 1951, 10 441

Degrees of pulmonary fat-embolism much more severe than that defined by Armin and Grant as "gross" are not uncommon in man[10] Certainly these are the cases in which fat-emboli are most likely to spread systemically, but it is also in such cases that changes due to pulmonary embolisation are liable to be erroneously ascribed to the effects of systemic involvement Although the pathological changes in the lungs—œdema, congestion, and hæmorrhage—are not in any way specific this does not exclude a causal relationship, and in any event the effects of pulmonary fat-embolism may be circulatory as well as respiratory[11] In my experience a predominantly intra-arteriolar and intra-arterial distribution of fat emboli in the lungs is often associated with a short survival time and an absence of systemic embolisation[10] Any system of grading the severity of embolisation should take cognisance of the size and situation of the emboli as well as of their numbers

While the arrest of fat emboli in the pulmonary vasculature undoubtedly protects the systemic circulation it can hardly be regarded as other than a pathological event, I submit that pulmonary fat-embolism should not be entirely discounted as a cause of illness and even death

University Department of Pathology
Western Infirmary,
Glasgow

A J WATSON

TRIGEMINAL NEURALGIA

SIR,—Professor Dechaume has very kindly sent me two papers[12 13] in which he cites the temporomandibular joint as a potential source of true trigeminal neuralgia I was unaware of these papers when I wrote my letter of Oct 1, and I apologise for that omission Professor Dechaume suggests a method of treatment which is new to me—namely, that the sympathetic enervation of the joint is an effective means of breaking into the vicious circle of effect aggravating cause

Colchester

MICHAEL FROST

NICOTINIC ACID IN ISCHÆMIC DISEASE

SIR,—Dr Archibald's criticism (Oct 8) of bus-drivers resuming their occupations after a coronary thrombosis is very pertinent, and it was only after very careful consideration that these drivers were allowed to go back to work Dr Archibald in effect poses the question "Should all patients who have had a coronary thrombosis be forbidden for that reason to drive a car?" With the usual treatment, I should be inclined to say "yes", but I would stress that there is a basic difference with the treatment described in my article of Sept 24

It is interesting that Hunter[14] has described results after nicotinic-acid therapy comparable with my own, except that his dosage is smaller, and he concludes that the improvement in angina is maintained so long as treatment is continued, and that angina gradually returns when treatment is stopped This is in accord with my experience over the fifteen years I have used this treatment, both after infarction and in angina, and it is for this reason that I came to the considered conclusion that ischæmic disease is probably a deficiency disease mainly of nicotinic acid, possibly also of pyridoxine (which forms a coenzyme mediating transaminase reactions and which is probably involved in the enzyme, glutamic-oxaloacetic transaminase) According to this concept, nicotinic acid is a physiological corrective of ischæmic disease

The first patient cited, who is an insurance agent, tells me he makes more than 100 calls a day in his car, and he has done this now for a long time The bus-drivers are seen and examined twice a quarter

Rothwell Haigh,
near Leeds

C E GOLDSBOROUGH

THE VERY DEAF CHILD

SIR,—The complaint of this school, which admits many children who have received various forms of home training, an important aspect of the work of most audiology clinics, is that the period before entry to school for most of them has been inadequately used

Of the present roll of 40 children, 32 have had preschool help of this kind, varying in length from six months to four years 30 of these children had hearing-aids issued by the clinics 2 were deemed too deaf to profit from an aid, though the parents of 1 bought a commercial model

Of the 31 with hearing-aids, only 4, however, were wearing them correctly—i e , continuously and at the right setting with an ear-mould which fitted sufficiently well to enable the necessary volume to be reached without acoustic feedback

At the moment of writing, 21 of the 31 children are wearing their aids properly both in and out of school with corresponding gains in speech improvement and language development Included in the 10 children who do not reach at home the standard of "hearing-aid usage" expected and obtained from them in school are all the 6 children with multiple handicaps The remaining 4 are among our most recent admissions

The fact that so many of these non-hearing-aid-users were trained within a relatively short space to regard their aids as an indispensable ally in their fight against deafness, and not as a barely tolerable encumbrance underlines the need to examine the weaknesses of a form of training which permits so much waste of valuable auditory training time

No teacher of the deaf, as far as I am aware, disputes the immense value of parent guidance and help to the children, particularly during the period between the diagnosis of deafness and the age of 2–3 years Many of us, however, believe that a special nursery school, fully equipped and staffed, where parents are free to come and go and take part in our work, where visiting otologists and psychologists can see the children in surroundings more appropriate than the clinical situation found in audiology units, offers not only the well-known advantages of nursery-school training but also permits conditions suitable for full-time educational and audiological help of the kind appropriate to the children's individual needs In addition, because continuous observation under controlled conditions is possible, it allows a more rapid and accurate assessment of the children's abilities and the nature and degree of their hearing loss, and enables future school placement to be considered on a better-informed basis

Such a special school should cooperate with local hearing schools for selected activities where the children of both schools can meet and play and, under skilled supervision, work with one another (*This is not difficult to arrange*—we do, in fact, work with 3 nearby hearing schools in Woodford in this way)

Miss Whetnall (Oct 15) has referred to the work of Wedenberg[1] who, for the initial period of auditory training, applies a live voice to the meatus of the deaf child without the use of an aid Unfortunately, she omitted to say that Wedenberg himself found that the best subjects for auditory training were the "*gifted children* (my italics) from groups 1a to 2a" (*i e* , children with considerable hearing for the important low frequencies, about 50 db at 250 and 500 cycles) and that children with much less hearing for low frequencies (groups 1b and 2b) were "difficult subjects even when their intelligence is high"

Of the children here for whom we have reliable audiograms 6 come within Wedenberg's groups 1a and 2a and of these 2 only are of above average intelligence

Even more significant is the fact that we are able to train children who Wedenberg found "difficult"—i e , the 1b and

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10 Watson A J Fat embolism Thesis University of Aberdeen 1960
11 Peltier L F *Surg Gynec Obstet* 1957, 104 313
12 Dechaume M Dore M Le Bars C., Rouot J *Rev Stomatol* 1950 51 157
13 Dechaume M *Dtsch Zahn Mund u Kieferheilk* 1959 31 69
14 Hunter J D *N Z med J* 1960 59 280

1 Wedenberg E *Acta laryngol Stockh* 1954 suppl 110 p 707

2b groups " whose sense of hearing is defined as non-functional for the ordinary purposes of life ",[2] into becoming talking children with normal attainments and a good command of language Only those, however, we have had from a very early age and who have no secondary handicap

If audiology clinics would transfer to the special nursery school or class at an early age the 1b and 2b children, and those of 1a and 2a group who are not receiving continuous or adequate auditory stimulation either at the meatus or through a hearing-aid, I for one should find less reason for complaint

Nursery School for Deaf Children,
Woodford Green Essex
B I INGALL

POTASSIUM IN THE TREATMENT OF CHOLERA

SIR,—In their article last week Dr Watten and Dr Phillips suggest that in the treatment of acutely ill patients 10 mEq (7 5 g) of potassium chloride should be added to 1 litre of saline solution The amount in grammes should read *0 75* This is no doubt a slip, but it is an important one Owing to the danger that this may be overlooked, libraries might consider making the correction on the article itself

Radcliffe Infirmary,
Oxford.
W I CRANSTON

ADMINISTRATION IN MENTAL HOSPITALS

SIR,—With great respect, I wonder whether Dr Kidd (Oct 29) has really found the ideal solution to the problem of medical administration in mental hospitals

As a medical superintendent, before the advent of the National Health Service and since, I have been trying to find the ideal relationship between the holder of that office and his senior colleagues for thirteen years, but have not succeeded yet, although I do not give up hope

We have worked a 3-team system here for ten years, and I support wholeheartedly the doctrine of full clinical freedom for all consultants, indeed, my consultant colleagues here have never complained to me of any interference with their work, but much tact and tolerance are needed on both sides if the hospital is to function smoothly as a corporate entity Dr Kidd tells us that he is responsible to his management committee for the efficiency of the medical work of the hospital How does he equate this personal responsibility with the " full responsibility " of his colleagues ?

One example will suffice How would he deal with a situation such as this, which could happen at almost any mental hospital, any day ? A fellow consultant admits, as an informal patient, an aggressive psychopath, who then rapes the small daughter of a hospital employee, resident on the estate I have been in office long enough to know that the Press, the general public, and indeed the management committee will look to one person only for an explanation, and that person is the unfortunate superintendent It will not help him to say that Dr So-and-So had " full responsibility "

The Mental Health Act has defined responsible medical officers as those in charge of the treatment of the patient Responsible to whom, and for what ? Does " treatment " include control of liberty, food, clothing, social and occupational activities, pocket money, and all the many other aspects of a patient's life ? If so, the result could be chaos with as many " systems " as there are consultants

The duties, responsibilities, and powers of medical superintendents have never been clearly defined No official guidance has been given, presumably in pursuance of the well-known technique of leaving decisions to the man on the spot, with the useful loophole of blaming him afterwards if trouble arises

Responsibility implies authority to take any necessary action, but the authority of the superintendent is vague in the extreme Now that consultants, rightly so, are undertaking greater responsibilities, the functions of the medical superintendent are more than ever in need of clarification This should be done as a matter of urgency, before there occurs some such trouble as that depicted above, with the inevitable recriminations which would follow

Superintendents have " carried the can " for a long time, but, in a changing world, it would be helpful to know something of its new contents

Bracebridge Heath Hospital,
near Lincoln
W A S FALLA

SIR,—Dr Kidd and his colleagues are to be congratulated on having accepted some of the principles without which a mental hospital continuing to have a medical superintendent can hardly be expected to function efficiently These are that the medical superintendent should do clinical work and do it on a basis of equality with his fellow consultants, without powers of interference in their work

I am afraid, however, that Dr Kidd's exposition of the medical superintendent's position in regard to administration involves apparent contradictions and several false or dubious premises, as exemplified by the suggestion that " as far as the hospital management committee is concerned he is answerable to them for the efficiency of the medical work of the hospital " I can only think that in this context " answerable " means " responsible " in which case the proposition is quite untenable A medical superintendent working on a basis of clinical equality with his fellow consultants and without powers of clinical interference cannot be " answerable " for the efficiency of the medical work of the hospital It is very relevant that the Mental Health Act, 1959, Memorandum on parts I, IV to VII and IX, paragraph 29, describes the " responsible medical officer " as " not responsible or answerable for the patient's treatment to any other doctor "

Dr Kidd, having listed various coordinating and facilitating functions of the medical superintendent, all of which, I suggest, can be done as well by the chairman of the medical advisory committee, goes on to say that such work can " perhaps be better done by a man who is permanently appointed to the office, because he has powers of decision and authority not available to an elected chairman of a medical staff committee " These powers and authority appear to derive from his being " officially recognised as responsible for medical organisation " This official recognition has the interesting—and highly undesirable—result that hospital management committees "have to take more notice of his monthly reports than the resolutions of medical advisory committees "

This is precisely the situation which consultants in many mental hospitals are no longer prepared to tolerate, especially in view of the fact that as from Nov 1 such hospitals will operate on the same basis as general hospitals All boards of governors of teaching hospitals and the management committees of most general hospitals recognise and " take notice " of their medical advisory committees as represented by an elected chairman Dr Kidd has made no case why management committees of mental hospitals should not do the same Such recognition should be based on the principle that the senior medical staff in any hospital have an equal and shared responsibility for reaching an agreed policy on all administrative matters affecting the hospital as a whole and that the essential administrative work of the medical superintendent or chairman of the medical advisory committee is to facilitate the carrying out of such agreed policy This may involve difficult negotiations with hospital management committee, regional hospital board, hospital officers, and others In such situations the

may be attributable to the very small dosage which they employed

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[2] *ibid* p 19 (reference to the definition issued by the Conference of Executives of American Schools for the Deaf, 1937)

Degrees of pulmonary fat-embolism much more severe than that defined by Armin and Grant as " gross " are not uncommon in man[10] Certainly these are the cases in which fat-emboli are most likely to spread systemically, but it is also in such cases that changes due to pulmonary embolisation are liable to be erroneously ascribed to the effects of systemic involvement Although the pathological changes in the lungs—œdema, congestion, and hæmorrhage—are not in any way specific this does not exclude a causal relationship, and in any event the effects of pulmonary fat-embolism may be circulatory as well as respiratory[11] In my experience a predominantly intra-arteriolar and intra-arterial distribution of fat emboli in the lungs is often associated with a short survival time and an absence of systemic embolisation[10] Any system of grading the severity of embolisation should take cognisance of the size and situation of the emboli as well as of their numbers

While the arrest of fat emboli in the pulmonary vasculature undoubtedly protects the systemic circulation it can hardly be regarded as other than a pathological event, I submit that pulmonary fat-embolism should not be entirely discounted as a cause of illness and even death

University Department of Pathology
Western Infirmary,
Glasgow

A J WATSON

TRIGEMINAL NEURALGIA

SIR,—Professor Dechaume has very kindly sent me two papers[12 13] in which he cites the temporomandibular joint as a potential source of true trigeminal neuralgia I was unaware of these papers when I wrote my letter of Oct 1, and I apologise for that omission Professor Dechaume suggests a method of treatment which is new to me—namely, that the sympathetic enervation of the joint is an effective means of breaking into the vicious circle of effect aggravating cause

Colchester

MICHAEL FROST

NICOTINIC ACID IN ISCHÆMIC DISEASE

SIR,—Dr Archibald's criticism (Oct 8) of bus-drivers resuming their occupations after a coronary thrombosis is very pertinent, and it was only after very careful consideration that these drivers were allowed to go back to work Dr Archibald in effect poses the question " Should all patients who have had a coronary thrombosis be forbidden for that reason to drive a car ?" With the usual treatment, I should be inclined to say " yes ", but I would stress that there is a basic difference with the treatment described in my article of Sept 24

It is interesting that Hunter[14] has described results after nicotinic-acid therapy comparable with my own, except that his dosage is smaller, and he concludes that the improvement in angina is maintained so long as treatment is continued, and that angina gradually returns when treatment is stopped This is in accord with my experience over the fifteen years I have used this treatment, both after infarction and in angina, and it is for this reason that I came to the considered conclusion *that ischæmic disease is probably a deficiency disease mainly of nicotinic acid, possibly also of pyridoxine* (which forms a coenzyme mediating transaminase reactions and which is probably involved in the enzyme, glutamic-oxaloacetic transaminase) *According to this concept, nicotinic acid is a physiological corrective of ischæmic disease*

The first patient cited, who is an insurance agent, tells me he makes more than 100 calls a day in his car, and he has done this now for a long time The bus-drivers are seen and examined twice a quarter

Rothwell Haigh,
near Leeds

C E GOLDSBOROUGH

THE VERY DEAF CHILD

SIR,—The complaint of this school, which admits many children who have received various forms of home training, an important aspect of the work of most audiology clinics, is that the period before entry to school for most of them has been inadequately used

Of the present roll of 40 children, 32 have had preschool help of this kind, varying in length from six months to four years 30 of these children had hearing-aids issued by the clinics 2 were deemed too deaf to profit from an aid, though the parents of 1 bought a commercial model

Of the 31 with hearing-aids, only 4, however, were wearing them correctly—i e , continuously and at the right setting with an ear-mould which fitted sufficiently well to enable the necessary volume to be reached without acoustic feedback

At the moment of writing, 21 of the 31 children are wearing their aids properly both in and out of school with corresponding gains in speech improvement and language development Included in the 10 children who do not reach at home the standard of " hearing-aid usage " expected and obtained from them in school are all the 6 children with multiple handicaps *The remaining 4 are among our most recent admissions*

The fact that so many of these non-hearing-aid-users were trained within a relatively short space to regard their aids as an indispensable ally in their fight against deafness, and not as a barely tolerable encumbrance underlines the need to examine the weaknesses of a form of training which permits so much waste of valuable auditory training time

No teacher of the deaf, as far as I am aware, disputes the immense value of parent guidance and help to the children, particularly during the period between the diagnosis of deafness and the age of 2–3 years Many of us, however, believe that a special nursery school, fully equipped and staffed, where parents are free to come and go and take part in our work, where visiting otologists and psychologists can see the children in surroundings more appropriate than the clinical situation found in audiology units, offers not only the well-known advantages of nursery-school training but also permits conditions suitable for full-time educational and audiological help of the kind appropriate to the children's individual needs In addition, because continuous observation under controlled conditions is possible, it allows a more rapid and accurate assessment of the children's abilities and the nature and degree of their hearing loss, and enables future school placement to be considered on a better-informed basis

Such a special school should cooperate with local hearing schools for selected activities where the children of both schools can meet and play and, under skilled supervision, work with one another (*This is not difficult to arrange*—we do, in fact, work with 3 nearby hearing schools in Woodford in this way)

Miss Whetnall (Oct 15) has referred to the work of Wedenberg[1] who, for the initial period of auditory training, applies a live voice to the meatus of the deaf child without the use of an aid Unfortunately, she omitted to say that Wedenberg himself found that the best subjects for auditory training were the "*gifted children* (my italics) from groups 1a to 2a " (i e , children with considerable hearing for the important low frequencies, about 50 db at 250 and 500 cycles) and that children with much less hearing for low frequencies (groups 1b and 2b) were " difficult subjects *even when their intelligence is high* "

Of the children here for whom we have reliable audiograms 6 come within Wedenberg's groups 1a and 2a and of these 2 only are of above average intelligence

Even more significant is the fact that we are able to train children who Wedenberg found " difficult '—i e , the 1b and

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[10] Watson A J Fat embolism Thesis University of Aberdeen 1960
[11] Peltier L F *Surg Gynec Obstet* 1957 104 313
[12] Dechaume M Dore M Le Bars C Rouot J *Rev Stomatol* 1950 51 157
[13] Dechaume M *Dtsch Zahn Mund u Kieferheilk* 1959 31, 69
[14] Hunter, J D *N Z med J* 1960 59 290

[1] Wedenberg E *Acta laryngol Stockh* 1954 suppl 110 p 707

2b groups " whose sense of hearing is defined as non-functional for the ordinary purposes of life ",[2] into becoming talking children with normal attainments and a good command of language Only those, however, we have had from a very early age and who have no secondary handicap

If audiology clinics would transfer to the special nursery school or class at an early age the 1b and 2b children, and those of 1a and 2a group who are not receiving continuous or adequate auditory stimulation either at the meatus or through a hearing-aid, I for one should find less reason for complaint

Nursery School for Deaf Children,
Woodford Green Essex

B I INGALL

POTASSIUM IN THE TREATMENT OF CHOLERA

SIR,—In their article last week Dr Watten and Dr Phillips suggest that in the treatment of acutely ill patients 10 mEq (7 5 g) of potassium chloride should be added to 1 litre of saline solution The amount in grammes should read *0 75* This is no doubt a slip, but it is an important one Owing to the danger that this may be overlooked, libraries might consider making the correction on the article itself

Radcliffe Infirmary
Oxford.

W I CRANSTON

ADMINISTRATION IN MENTAL HOSPITALS

SIR,—With great respect, I wonder whether Dr Kidd (Oct 29) has really found the ideal solution to the problem of medical administration in mental hospitals

As a medical superintendent, before the advent of the National Health Service and since, I have been trying to find the ideal relationship between the holder of that office and his senior colleagues for thirteen years, but have not succeeded yet, although I do not give up hope

We have worked a 3-team system here for ten years, and I support wholeheartedly the doctrine of full clinical freedom for all consultants, indeed, my consultant colleagues here have never complained to me of any interference with their work, but much tact and tolerance are needed on both sides if the hospital is to function smoothly as a corporate entity Dr Kidd tells us that he is responsible to his management committee for the efficiency of the medical work of the hospital How does he equate this personal responsibility with the " full responsibility ' of his colleagues ?

One example will suffice How would he deal with a situation such as this, which could happen at almost any mental hospital, any day ? A fellow consultant admits, as an informal patient, an aggressive psychopath, who then rapes the small daughter of a hospital employee, resident on the estate I have been in office long enough to know that the Press, the general public, and indeed the management committee will look to one person only for an explanation, and that person is the unfortunate superintendent It will not help him to say that Dr So-and-So had " full responsibility "

The Mental Health Act has defined responsible medical officers as those in charge of the treatment of the patient Responsible to whom, and for what ? Does ' treatment " include control of liberty, food, clothing, social and occupational activities, pocket money, and all the many other aspects of a patient s life ? If so, the result could be chaos with as many " systems " as there are consultants

The duties, responsibilities, and powers of medical superintendents have never been clearly defined No official guidance has been given, presumably in pursuance of the well-known technique of leaving decisions to the man on the spot, with the useful loophole of blaming him afterwards if trouble arises

Responsibility implies authority to take any necessary action, but the authority of the superintendent is vague in the extreme Now that consultants, rightly so, are undertaking greater responsibilities, the functions of the medical superintendent are more than ever in need of clarification This should be done as a matter of urgency, before there occurs some such trouble as that depicted above, with the inevitable recriminations which would follow

Superintendents have " carried the can " for a long time, but, in a changing world, it would be helpful to know something of its new contents

Bracebridge Heath Hospital,
near Lincoln

W A S FALLA

SIR,—Dr Kidd and his colleagues are to be congratulated on having accepted some of the principles without which a mental hospital continuing to have a medical superintendent can hardly be expected to function efficiently These are that the medical superintendent should do clinical work and do it on a basis of equality with his fellow consultants, without powers of interference in their work

I am afraid, however, that Dr Kidd's exposition of the medical superintendent's position in regard to administration involves apparent contradictions and several false or dubious premises, as exemplified by the suggestion that " as far as the hospital management committee is concerned he is answerable to them for the efficiency of the medical work of the hospital " I can only think that in this context " answerable " means " responsible " in which case the proposition is quite untenable A medical superintendent working on a basis of clinical equality with his fellow consultants and without powers of clinical interference cannot be " answerable " for the efficiency of the medical work of the hospital It is very relevant that the Mental Health Act, 1959, Memorandum on parts I, IV to VII and IX, paragraph 29, describes the " responsible medical officer " as " not responsible or answerable for the patient's treatment to any other doctor "

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This is precisely the situation which consultants in many mental hospitals are no longer prepared to tolerate, especially in view of the fact that as from Nov 1 such hospitals will operate on the same basis as general hospitals All boards of governors of teaching hospitals and the management committees of most general hospitals recognise and " take notice " of their medical advisory committees as represented by an elected chairman Dr Kidd has made no case why management committees of mental hospitals should not do the same Such recognition should be based on the principle that the senior medical staff in any hospital have an equal and shared responsibility for reaching an agreed policy on all administrative matters affecting the hospital as a whole and that the essential administrative work of the medical superintendent or chairman of the medical advisory committee is to facilitate the carrying out of such agreed policy This may involve difficult negotiations with hospital management committee, regional hospital board, hospital officers, and others In such situations the

elected chairman of the medical advisory committee, speaking for the medical staff, *should* carry more weight than a permanently appointed medical superintendent none of whose authority derives from his colleagues.

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[2] *ibid* p 19 (reference to the definition issued by the Conference of Executives of American Schools for the Deaf, 1937)

It will be a pity if the tremendous opportunities for advance offered to mental hospitals by the Mental Health Act are lost by a refusal to accept the above basic principles of hospital administration.

Shenley Hospital,
near St. Albans, Herts.
D. BARDON

OBSTETRIC FLYING-SQUADS

SIR,—Dr. Vartan's letter of Oct. 22 appears to be misdirected, inappropriate and unreasonable. Has no-one ever told him that normal childbirth is a physiological process? To compare it with an operation for varicose veins betrays a distortion of outlook which is all too common.

Hove.
F. V. GRIFFITHS

RADIOCHEMICAL SYNTHESIS OF TRIIODOTHYRONINE

SIR,—Dr. Deutsch (Sept. 10) draws attention to the possible formation of ^{131}I-labelled triiodothyronine by the decay of a molecule of thyroxine containing two ^{131}I atoms, and, with this in mind, discusses the results of Gross and Pitt-Rivers [1-3] and of Braasch et al.[4] His conclusions assume that in these experiments a substantial number of doubly labelled thyroxine molecules is present. Certainly, as regards the work of Gross and Pitt-Rivers, this assumption is incorrect.

The relative numbers of doubly and singly labelled molecules depend on the relative numbers of radioactive (^{131}I) and stable (^{127}I) atoms of iodine present. The position can be more easily illustrated by referring to ^{131}I thyroxine synthesised in vitro by an exchange reaction. In this material labelling can take place in only two atoms, those in the 3′,5′ positions, and not in all four atoms as in the material synthesised in vivo from ^{131}I iodide. Mr. Holloway and Mrs. Pitt-Rivers (Oct. 22) refer to the work of Tata[5] on decomposition products of ^{131}I-labelled thyroxine supplied by Abbott Laboratories. Assuming that this materal is prepared by the method of Gleason,[6] and that it is not diluted with inactive thyroxine after preparation, we calculate, from the quoted maximum specific activity of 50 mC per mg. thyroxine, that 1 mC of ^{131}I is associated with 6·5 µg. of iodine in the 3′,5′ positions. The weight of 1 mC of isotopically pure ^{131}I is 8×10^{-3} µg., and therefore in the 3′,5′ positions of this product 1 atom of ^{131}I is present to approximately 1000 atoms of ^{127}I. This means that for every 2000 singly labelled molecules only 1 is doubly labelled. No detectable amount of ^{131}I-labelled triiodothyronine is therefore likely to arise by the process postulated by Deutsch, and the fact that no ^{131}I-labelled triiodothyronine was detected in Tata's work gives us no information on the correctness or otherwise of Deutsch's postulate.

The position regarding in-vivo syntheses is more complex. Inactive iodine may be present in the so-called "carrier-free" ^{131}I iodide, and dilution with further inactive material may take place during transport in the body to the thyroid gland, and in the thyroid gland itself. Before 1954, ^{131}I produced in Great Britain had a specific activity of about 1 mC per µg. iodine: this implies that about 1 in every 100 atoms of iodine present was radioactive. It was this material that was used in the work of Gross and Pitt-Rivers. Even had no further dilution taken place in the subjects the number of multiple (i.e., double, triple, or quadruple) labelled molecules would be too small to yield a significant amount of ^{131}I-labelled triiodothyronines by decay (assuming that ^{131}I atoms are randomly distributed in the 4 positions of thyroxine, multiple-labelled molecules would form about 1·5% of the total labelled molecules).

The specific activity of ^{131}I produced in Great Britain has increased markedly since 1954. The Radiochemical Centre product is specified as being not less than 10 mC per µg. iodine, and individual batches have given 20 mC per µg. iodine: this latter figure corresponds to 1 atom of ^{131}I in 6 atoms of iodine. The proportion of ^{131}I atoms in fission product ^{131}I supplied by Oak Ridge is probably even higher. Rupp et al.[7] suggest 1 atom of ^{131}I to 1 atom of ^{129}I plus ^{127}I (^{129}I is sufficiently long lived to be considered stable). With material of such high specific activity any dilution with stable iodine in the body before thyroxine synthesis becomes specially important. The factors determining the extent of such dilution are too complex for discussion other than by an expert in the field. In general it seems reasonable to suppose that the extent of dilution will be relatively large. In certain cases this may not be so, and ^{131}I-labelled triiodothyronine might arise in the manner postulated by Deutsch.

Radiochemical Centre,
Amersham.
J. C. CHARLTON

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1. Gross, J., Pitt-Rivers, R. *Lancet*, 1951, ii, 766.
2. Gross, J., Pitt-Rivers, R. *ibid.* 1952, i, 439.
3. Gross, J., Pitt-Rivers, R. *Biochem. J.* 1953, 53, 645.
4. Braasch, J. W., Flock, E. V., Albert, A. *Endocrinology*, 1954, 55, 768.
5. Tata, J. R. *Clin. chim. acta*, 1959, 4, 427.
6. Gleason, G. I. *J. biol. Chem.* 1955, 213, 837.
7. Rupp, A. F., Beauchamp, E. E., Farmakes, J. R. United States Atomic Energy Commission document ORNL-1047. Production of Fission Product Iodine 131.

PERITONEAL SPLASH: A PHYSICAL SIGN

SIR,—Mr. F. G. Smiddy (Oct. 15) points out that this physical sign can be elicited only in the anæsthetised patient. Many years ago, when I saw more patients with perforated peptic ulcer than I do now, I noticed that in some it was possible to detect a splash while percussing for free gas in the peritoneal cavity. Light and careful percussion in the line of the right nipple with the patient prone will in many cases reveal the gas bubble which obliterates the band of dullness over the liver. At the lower edge of the bubble the pleximeter finger detects a faint splash as the abdominal wall comes into contact with the surface of the fluid behind the bubble. This sign is easily elicited when the perforation is large, there is much effusion in the peritoneal cavity, and the rigidity of the abdominal wall is less than board-like. But then the diagnosis can more confidently be made by other means. In the early case with a small hole, little effusion, and a rigid abdominal wall the sign is not easily elicited.

I concluded that as a physical sign it was of little value, but when present it provided a comforting confirmation of the diagnosis.

Whiston Hospital,
Prescot, Lancs.
J. A. MARTINEZ

SIDE-EFFECTS OF LIBRIUM

SIR,—I read with close attention the correspondence that followed the letter by Dr. Ingram and Dr. Timbury (Oct. 1) about the new drug methaminodiazepoxide ('Librium').

My mind was certainly imbued with that attitude of scepticism and circumspection favoured by your correspondents when I first prescribed these capsules for patients with anxiety states, since I had seen in recent years the much-vaunted advent of a glut of new drugs, the great majority of which were destined to find ere long a dusty tomb on some neglected shelf of the dispensary. I soon came to the conclusion, however, that librium is of much value in the anxiety states. Considerable benefit was obtained in some 5 out of 10 sufferers from morbid anxiety, a result which was the more impressive because not a few of them had previously had little or no relief from other calmative drugs—which clearly mitigates the influence of suggestion. A large majority of those responding to the drug need take the relatively modest dose of 10 mg. three times daily to gain relief from their emotional tension, disagreeable side-effects being exceptional in such circumstances Some of these patients remarked that, unlike other drugs they had tried, librium suppressed their anxiety without producing troublesome somnolence In my hands, the drug has proved more useful for the assuagement of diffuse anxiety than for the relief of the specific phobias of the obsessional neuroses

Although it would doubtless be prudent to postpone *final* judgment I am confident that this drug will soon win its spurs in general practice, and thereby materially reduce the number of cases of anxiety state referred to psychiatric out-patient clinics

Menston Hospital,
Ilkley, Yorks

J TODD

HEPATIC SIZE, SHAPE, AND CONTENT

SIR,—We must be grateful for having been reminded of the advantages of peritoneoscopy Though too seldom practised in this country, its value in the diagnosis of hepatic disease and anatomical abnormalities must be recognised

For the certain exclusion of disease, however, it is not so reliable, and this and its other limitations seem to me to indicate the desirability of laparotomy in determining that no hidden metastases are present in the liver

Churchill Hospital,
Headington, Oxford

C GRIMSHAW

NEGATIVE ASSOCIATION OF ABO BLOOD-GROUPS WITH FRACTURED HIP

SIR,—In your issue of Aug 13, Dr Wiener said that Buchwalter had observed an excess of blood-group A in patients with fractured femurs We note that Buchwalter [1] has investigated the ABO blood-group distribution in 910 cases of fractured hips and found no statistical difference when compared with a control group We have examined a small series of patients who had been treated for fractured femoral necks at this hospital All these patients had been blood-grouped on admission as a matter of routine

TABLE I—ABO BLOOD-GROUP DISTRIBUTION

Group	Control series	Intertrochanteric fracture group	Other femoral neck fractures	Total test series
A	1906 *(32 3%)*	56 *(42 8%)*	73 *(33 5%)*	129 *(37 0%)*
B	637 *(10 8%)*	9 *(6 9%)*	22 *(10 1%)*	31 *(8 9%)*
AB	178 *(3 0%)*	2 *(1 5%)*	6 *(2 7%)*	8 *(2 3%)*
O	3177 *(53 9%)*	64 *(48 8%)*	117 *(53 7%)*	181 *(51 8%)*
Total	5898	131	218	349

TABLE II—DISTRIBUTION OF THE RHESUS FACTOR

Rhesus	Control series	Fracture series
Positive	344 *(80 6%)*	279 *(79 9%)*
Negative	83 *(19 4%)*	70 *(20 1%)*
Total	427	349

Table I shows the ABO groups of these 349 patients and those of the control series compiled from data from 5898 consecutive new donor registrations with the West of Scotland Regional Blood Transfusion Service The patients were further subdivided into intertrochanteric fractures and other femoral neck fractures This small series reveals that there is no significant difference in ABO blood-group distribution, although one may be impressed by the relatively high incidence of group A in the intertrochanteric fracture group, there is no statistical difference ($p = 1\ 3$) Furthermore, table II shows that there is again no significant difference in the incidence of the rhesus factor in the fracture patients and those of a small control series of 427 donors

We wish to thank Dr I A Cook, Mr W Sillar, and Dr J Wallace for assistance, and Dr R A Robb for his statistical help

J MALCOLM CAMERON
A G MELROSE
G A WHITEFIELD

Southern General Hospital
Glasgow

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[1] Buchwalter, J A *Acta genet* 1957, 6, 561

MODERN CLINICAL BIOCHEMISTRY

SIR,—Professor Cappell's presidential address (Oct 15) has called forth a prompt and explosive comment (Oct 29, p 985) from his biochemical colleague at the Western Infirmary

As a biochemist, Dr Hendry is naturally most concerned with Professor Cappell's assessment of the position of chemical pathology in the framework of clinical pathology, and there can be little doubt that he has voiced the feelings of many of the medical and non-medical biochemists who have entered or considered entering the hospital laboratory service These feelings are clearly expressed in their reluctance to apply for posts If Dr Hendry as the head of a teaching-hospital biochemistry department can say it is all but impossible to recruit young science graduates into hospital biochemistry departments, how much more so is this the case in regard to the non-teaching hospitals administered by regional boards, and this at a time when scientists are making fundamental contributions in every branch of industry and many other fields of activity Why should the hospital service alone be denied this advantage? Surely the health of the nation should have at least an equal call on the scientific potential No medical man can view this situation with equanimity, and least of all pathologists whose own work can gain so much more significance and value by close collaboration with chemical studies It would seem worth trying to find the explanation for the unpopularity of hospital work for science graduates

Firstly, the newly graduated chemist, if he is worth his salt, will wish to advance his knowledge and status by acquiring a postgraduate qualification This requires in the case of a PH D that the department in which he works will be recognised by a university department of chemistry or biochemistry as giving proper facilities for postgraduate study together with supervision by a senior member of the staff of these departments In the case of an M SC no university supervision is required, but unless the proper facilities are there the preparation of a thesis will be impossible These facilities consist above all in adequate time—and, in the case of more senior biochemists, assistance—to pursue a research project, and there seems no doubt that the greatest drawback to the hospital biochemistry service in the eyes of would-be graduate recruits is the lack of time and encouragement to undertake research Many pathologists consider biochemical research inappropriate in hospital laboratories, especially in non-teaching hospitals, or, even if they are convinced of its value, are unable to persuade hospital management committees to provide sufficient staff to enable the biochemical graduate to devote time to original investigations He is consequently inundated with routine and repetitive work and soon becomes dispirited and leaves the service, or stays on disgruntled with a grudge against doctors in general and pathologists in particular

No greater catastrophe could befall the pathologist than to lose that intimate contact with the biochemist which promises to solve many problems which neither can solve alone Yet it is clear from Dr Hendry's letter that the pathologists' laudable attempts to weld the hospital laboratory disciplines into a single integrated team are viewed with the greatest suspicion by medically and non-medically qualified biochemists alike The reason for this lies in the question of prospects The young biochemist is not going to sit back and vegetate when he has obtained his postgraduate qualifications He hopes eventually to attain as senior and respected a position in the hierarchy of the hospital staff as he would in industry or other Government scientific establishments, and to have a reasonable chance of running his own department Under the present circumstances he will find his way blocked in both these directions He cannot obtain status comparable with his medical colleagues as long as his method of appointment is that of registrars, technicians, and radiographers—viz, by hospital management committees and not by regional boards Neither can he obtain it—human nature being what it is—as long as his salary is so much less than that of his medical colleagues that he cannot join fully with them in social activities and educate his children similarly As for running his own department, it is generally believed that the Association of Clinical Pathologists considers that the biochemist should be directly responsible to the head of the laboratory in which he works (i e, the senior clinical pathologist), though I am not aware of any published statement of this policy While not suggesting that a non-medical biochemist should be in charge of the other clinical pathological laboratories, I am at a loss to see why a senior biochemist, whether medical or non-medical, should not be in absolute charge of his department, responsible only to the employing authority Of course there will be many matters of a clinical nature which he will want to discuss with the medical pathologists, but surely discussion on terms of parity is the essence of the teamwork which we wish to see in the integrated department of clinical pathology of the future

Yet another explanation for the mistrust by biochemists of pathologists lies in the manner in which the latter are organised for political purposes The Association of Clinical Pathologists has only medically qualified full members How can it be representative of biochemists in general? If it wishes to be considered thus representative, it must give full membership to all hospital biochemists of suitable seniority (which would seem appropriate enough if hospital biochemistry is indeed a branch of clinical pathology!) Similarly if pathological advisory committees wish to be considered qualified to advise regional boards on biochemical matters they should admit senior non-medical biochemists to membership If these suggestions are not attractive to pathologists, would it not be better for them to leave the advising on biochemical matters to the Association of Clinical Biochemists on the one hand and to regional biochemistry advisory committees, still to be formed, on the other? While retaining their role of principal advisor to the authorities on biochemical matters, these organisations would no doubt welcome and benefit by periodic discussions through joint consultative committees with the corresponding pathological bodies

In the meantime, the recruiting position has deteriorated to a stage where it is impossible to fill biochemical appointments even with candidates who are far from ideal There is here a vicious circle The poor quality of the majority of science graduates accepting posts in the hospital biochemistry service has prevented many pathologists from gaining insight into the reliability and potentialities of the best type of biochemist Otherwise it is possible that a far greater degree of responsibility and scope would have been accorded the science graduate Now it is too late, and in despair the pathologists have turned to the young men of their own profession to fill the gap Although there is much that is attractive in the medically qualified biochemist (chemical pathologist), the disadvantages would seem far to outweigh the advantages if he is only going to have one year of fundamental study in chemistry as Professor Cappell suggests With so little experience in chemistry, how will he be able to attract to work under him keen young scientists just leaving university departments of chemistry four years after they have taken their advanced level G C E? If he does not attract them, the standing of our departments of chemical pathology will fall below those of departments of clinical chemistry in other countries

I would suggest it would be far more long-sighted to make the hospital biochemical service attractive to the best young brains in chemistry and biochemistry by introducing the following innovations

(*a*) Every biochemist post advertised (or at least a considerable proportion, which should be specially designated as largely free from routine and repetitive work) should carry with it (i) facilities for obtaining a postgraduate qualification, (ii) reasonable opportunity to reach status comparable in salary and independence with that of medical consultants,

(*b*) *Research should be considered a normal and not an* exceptional activity of biochemistry departments

(*c*) Appointments to senior (principal and top-grade) biochemical posts should be made by regional boards

(*d*) Biochemistry advisory committees should be appointed by regional boards and should always include a professor of chemistry or biochemistry

Although there are many other ways in which hospital biochemistry could be made more attractive, if those mentioned here are implemented there would surely be a most gratifying influx of the best type of scientist into the service, and I should like to see pathologists taking the lead in securing these improvements because it is they who will gain most by having the privilege of working as a team in close collaboration with the finest products of our universities' scientific departments

Midland Centre for Neurosurgery,
Smethwick

A L WOOLF

CHROMOSOME ANALYSIS

SIR,—I was surprised by Dr Stewart's letter of Sept 17 From his statements, one may conclude that colchicine and its derivatives causes heteroploidy and triploidy in animals So far as I am aware, the few cases of heteroploidy and triploidy observed in animals were associated with a highly artificial technique

Colchicine was added to sperm material and the animals artificially inseminated In this way, a few rabbits and one pig supposed to be triploids were obtained[1, 2] However, the accounts concerning these animals have been criticised and their triploid nature is unconvincing and not yet established[3] To sum up, it is apparent from these reports that no polyploid animals have been produced by colchicine[4] Moreover, colchicine does not cause gene mutation[5]

Recently, by intrauterine injections of colchicine into female mice just before mating, Edwards obtained some heteroploid embryos at 3½ days' gestation Chromosome counts of the mature offspring of these females, however, showed no heteroploids[6] Using a different technique, similar results were obtained in rats by French workers A few "heteroploid" embryos were seen at 12th day but none at full-term gestation[7]

The method is, I believe, simple and useful The results are good, and nothing suggests that the intravenous administration of the colchicine derivative is

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1 Melander Y *Hereditas* 1950 36 335 *ibid* 1951 37 288
2 Häggkvist, G Bane A *ibid* 1950 36 329
3 White M J D *Animal Cytology and Evolution* Cambridge, 1954
4 Eigsti O J Dustin P Jr Colchicine Iowa 1957
5 Dobzhansky T Genetics and the Origin of Species New York, 1951
6 Edwards R G *J exp Zool* 1958 137 317 *ibid* p 349
7 Piko, L., Bomsel Helmreich O *Nature Lond* 1960, 186 737

dangerous So far we have used the drug in 62 patients without any toxic manifestation

Department of Clinical Medicine,
Medical School of Ribeirao Preto,
Sao Paulo, Brazil
CÁSSIO BOTTURA

TREATMENT OF IDIOPATHIC HYPERCALCÆMIA OF INFANTS

SIR,—Many articles have now appeared about the treatment of idiopathic hypercalcæmia of infants A low calcium and vitamin-D intake, a high phytate intake, and the administration of cortisone have been recommended To my knowledge mention has not been made of the possible beneficial effect of total exclusion from ultraviolet rays

The antirachitic effect of sunlight is thought to be due to the activation of 7-dehydrocholesterol in skin This activation may result in the formation of substances with vitamin-D activity equivalent to 1000 or more units of vitamin D per day in infants who are exposed to ultraviolet radiation Possibly this disease has not been reported in Negroes because of the lesser effect of ultraviolet rays on deeply pigmented skin

It seems probable that infants with idiopathic hypercalcæmia are sensitive to very small amounts of vitamin D and it would seem advisable that patients with this disease be excluded from sunlight during those seasons when rays between 280 and 320 µ are present.

Possibly someone with knowledge of the metabolism of vitamin D might render judgment whether infants with idiopathic hypercalcæmia should be excluded from sunlight as part of their treatment

Department of Pediatrics,
Jefferson Medical College,
Philadelphia.
HANS G KEITEL

TREATMENT OF OBESITY BY THE HIGH-FAT DIET

SIR,—Bearing in mind case 5, and the large group of patients and friends she appears to represent, can Prof Yudkin and Miss Carey (Oct. 29) offer a 1500-calorie diet that is *permanently* acceptable both *socially* and financially to an adult woman of any age? An overweight woman is conspicuous in a crowd she does not wish to draw further attention to herself by always differing from the group when she is not eating alone

We would be most grateful

Hadleigh, Essex.
DAPHNE SASIENI

ERYTHROCYTE ENZYME DEFICIENCY IN UNEXPLAINED KERNICTERUS

SIR,—I was very interested by the contributions from Smith and Vella[1] and Doxiadis et al.[2] They confirm some observations I had the opportunity to report[3–6] last year

I have so far studied 19 jaundiced newborn children (11 males, 8 females) with unstable G S.H. and/or G -6-P D defect in their erythrocytes In 10 cases exchange transfusion was performed 7 of the transfused children and none of the untreated survived without damage Precipitating factors, such as dangerous drugs, were recognised in only a few cases Severe anæmia was rarely present, on the other hand, jaundice was often associated with severe clotting disturbances, indicating perhaps hepatic impairment, which may be due to the enzyme abnormality itself In fact, as I was able to demonstrate by liver biopsy, G -6-P D activity is decreased in the liver of sensitive individuals as well as in their erythrocytes[6] The observations of Smith and Vella and Doxiadis et al emphasise again the importance of this particular type of neonatal jaundice They also confirm the high incidence of the syndrome in a few families bearing the defect, and this fact suggests that there is a genetic factor in addition to the G -6-P D defect.

Clinica Pediatrica,
Università di Sassari,
Italy
FRANCO PANIZON

A SEVERE ANAPHYLACTOID REACTION TO HYDROCORTISONE

SIR,—Occasional allergic reactions following the local injection of hydrocortisone have been recorded,[1] and in many cases the possibility that associated use of hyaluronidase or procaine was to blame has not been firmly excluded The following case illustrates an allergic response of alarming severity to the injection of 'Hydrocortisyl' (Roussel) 5 ml in a patient who had never had either local or general steroid medication.

No other solution was injected and it was possible to exclude any previous injections (within 2 months) and any tablets or medicines (except 2 tab codein co B P, to which the patient was accustomed, taken a week previously) Similarly no dietary explanation could be discovered

A woman of 50 had, on April 8, 1960, a cup arthroplasty for osteoarthritis of the right hip She made a normal recovery, and was discharged to outpatients on June 17

On Sept 15, during follow-up examination, she complained of pain in the right shoulder A typical moderately severe supraspinatus tendinitis, with early pericapsulitis, was found, and at about 3.30 P M hydrocortisyl 5 ml was injected into the rotator cuff

She had no immediate ill effects, but at 7 30 P M, after supper, she suddenly felt her "face funny—blotchy with lumps, and burning" Red patches appeared on her arms, and she felt sick. She "passed out" and was carried to bed

An hour later, when her doctor arrived, she had regained consciousness, but she was vomiting profusely, had pain in the stomach and loins, and had urticaria, especially on the arms and face Conglomerate petechiæ and bruises appeared over the arms and face She was in a state of shock, with tachycardia, extrasystoles, and a weak pulse. There was much abdominal tenderness, especially in the liver area

She was given anti-histamines ('Piriton'), and she felt a bit better next day, but for 2 days she vomited repeatedly and had diarrhœa and rectal incontinence The stools were fluid and black, and the vomit contained dark blood

She was readmitted to hospital on the 3rd day Laboratory investigations showed hæmoglobin 92%, platelets 300,000 per c.mm, bleeding-time 2 min, clotting-time 6 min, clot retraction after 1 hour normal, prothrombin content 100% of normal, and prothrombin consumption normal The vomit contained dark blood, and occult blood was present in the stools The urine was normal.

Vomiting and diarrhœa ceased on the day of admission, and the abdominal pain and tenderness cleared up within 48 hours She returned home after 5 days

Although intradermal skin tests were unlikely to be helpful so soon after such a severe reaction, they were attempted on Sept. 7 using (1) control solution, (2) a minute dose of penicillin (to exclude penicillin contamination of the syringe used for injection), and (3) hydrocortisyl 0 01 ml An erythematous plaque 0 75 cm. in diameter formed in 24 hours around the site of hydrocortisyl injection, and persisted for 2 weeks, while the control sites showed no reaction

Thus it appears almost certain that this alarming reaction was due to the hydrocortisyl injection. Some

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[1] Smith, G Vella F *Lancet* 1960, i 1133
[2] Doxiadis S A, Fessas P Valaes T *ibid* July 2, 1960, p 44
[3] *Studi Sassaresi*, 1959 37 19
[4] *Acta pædiat latina*, 1959 12, 904
[5] XVII Congrès des Pédiatres de Langue Française, Oct. 1959, vol IV Montpelier
[6] *Boll Soc Ital Biolo Sper* 1960 36, 106

[1] Kendall, P H. *Ann phys Med* 1958, 4, 170

2000 hydrocortisyl injections have been given in this department over the past 3 years, and except for one case of mild infection following an injection for tennis elbow no other ill effects have been encountered from the use of these injections for the minor orthopædic troubles treated by this method

My thanks are due to Dr Josef Grutz, who dealt with this emergency so capably, and who has cooperated in the inquiry concerning ætiological possibilities

Oldchurch Hospital,
Romford, Essex
R A KING

ZOLLINGER-ELLISON SYNDROME

SIR,—With great interest I read the article in your issue of July 16 concerning this syndrome with diarrhœa and malabsorption The gastric-secretion studies before and after removal of the pancreatic islet-cell tumour were particularly striking As the Birmingham group point out, confirmation of their observation with tumours of similar type is important, so you may be interested in the story of a patient Dr G J Verdonk and I reported[1] at a colloquium of gastroenterology in Antwerp in September, 1958

A 66-year-old woman who presented herself in June, 1957, had a continuous pain in the epigastrium, spreading to the back After meals the pain was worse and she complained of heartburn and eructation She had no diarrhœa—on the contrary there was a distinct constipation She never had hypoglycæmic attacks

Examination of this fat healthy-looking woman revealed a resistance in the left upper abdomen which was at first thought to be an enlarged spleen

Erythrocyte-sedimentation rate 15 mm in one hour Hæmoglobin 12 8 g per 100 ml White cells 5400 per c mm, normal differential count Liver-function test normal No occult blood in the fæces Urine normal A fractional test-meal showed considerable hyperacidity free acid 106, total acid 120

X-ray examination of the stomach did not demonstrate an ulcer, but the mucous-membrane pattern was rough On compression of the stomach an area of lack of contrast was visible, possibly caused by pressure from behind The radiologist suggested a pancreatic tumour or cyst Just distal to the duodenal bulb a pseudopodial contour was seen, interpreted as a diverticulum

After six weeks' ulcer treatment with rest, diet, antispasmodics, sedatives, and antacids she was admitted to hospital, because the abdominal mass was still palpable We finally decided on operation On Nov 1, 1957, a pancreatic tumour, 7×6 5×6 5 cm, was removed During the operation the stomach and intestines could not be explored The surroundings of the tumour and omentum were hyperæmic and contained large dilated veins The omentum was containing the tumour and was firmly connected to the surface of the spleen The tumour was removed without vagtomy or gastrectomy The histological diagnosis was "insulinoma"

In September, 1958, nearly ten months after the operation, a fractional test-meal showed that the acid secretion was now reduced to subnormal free acid 0, total acid 16 (maximum)

Municipal Hospital,
Arnhem, Holland
M DIJK

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[1] Dijk, M, Verdonk G J *Tijdschr Gastro enterologie*, 1958, 1, 481

The Widdicombe File

LXVII —THE DIVISION OF PATHOLOGISTS

DEAR PETER,

I too thought your letter was sound but I think your friend G G, like several of the pathologists, is not entirely familiar with the real function of a college They ask "Can we trust the physicians", meaning presumably the internists, the dermatologists, the pædiatricians, the neurologists, the psychiatrists, and the other *clinicians* in the college, and they talk earnestly about the need for independence But, bless our souls, why do they need to be independent? A college is basically a degree-granting body and also ideally a community of individuals with kindred interests Do we hesitate to take a university medical degree because we doubt the good intentions of the philosophers or theologists who are represented in its court, or do we demand independence so as not to have to eat at table with engineers or lawyers? Maybe the young men want independence at any price because this is the parrot cry of the mid 20th century Fortunately in the college the dermatologists seem to show no distrust of the psychiatrists, and the neurologists are not afraid of being outvoted by the general physicians else there would have to be lots of new colleges What will it benefit the pathologists of tomorrow to have their own college with its expensive library and regalia, portraits and plate? Are pathologists anxious to accept the social and other obligations of a college and to maintain an expensive establishment—for rest assured they will not for long remain content with an attic in Euston but will feel the urge to compete on the perimeter of Regents Park?

Although your arguments were sound one correspondent accused you of talking nonsense His letter reveals the lack of cohesion amongst pathologists and indeed the seed of the next potential split ("Can we consultant biochemists trust the pathologists and bacteriologists?—we must be independent at all costs") What I mean is this, Peter, if the pathologists (and I am using this term generally to include bacteriologists, virologists, chemical pathologists, serologists, forensic pathologists, and hæmatologists—all in fact who are concerned with the laboratory investigation of the patient alive or dead) do not accept this very generous offer of negotiation by the Royal College of Physicians (some claim that it will fail because it is too generous), they may have to wait a long time before achieving the unanimity they require to embark on a new venture Many of the academic pathologists—if what I hear is true—care little whether there is a faculty of the college or a new college

Please impress on your many pathologist friends, Peter, that a faculty will require an appreciable measure of support but a new college will require overwhelming support from all species of pathologists Remind them that a faculty can always be dissolved (I trust that in the event of a faculty both the pathologists and the college will insist on having this in their agreement) but once they embark on a college they will have committed their successors to a life of independence and will have severed connection with their clinical colleagues A recent president of the college, it is said, once invited the pathologists to look forward fifty years They should do this now The rapid growth of specialism, automation, and the increasing excellence of technicians may bring the pathologist of the future much nearer to the patient than he is today and nearer to the clinicians An irrevocable move at this time would be a misfortune

Yours ever,
W W

Parliament

Queen's Speech

In the Speech from the Throne at the opening of Parliament on Nov. 1 it was announced that the Government proposed to increase war pensions, and retirement pensions, other benefits, and contributions under the National Insurance schemes.* They would authorise an increasing level of expenditure on the physical recreation of the young. Awards for students at universities and for those taking comparable courses at other institutions of higher education would be granted on an improved basis. They would introduce a Bill to provide better means of dealing with young offenders, to extend compulsory after-care to prisoners and so to discourage them from reverting to crime, and to improve the management of approved schools.†

Welsh Teaching Hospital

On Nov. 2, on the adjournment, Mr LEO ABSE sharply criticised the plans for this new teaching hospital, which he described as an "ossified hospital design accepted from a septuagenarian architect by assessors led by another septuagenarian architect . . . a design for a hospital for 1950, not as it should be for a 1980 hospital." Wales wanted a forward-looking teaching hospital, it was being proffered a mausoleum.

Going on to offer detailed criticisms, he said that the contemptuous attitude to research was well illustrated by the location and space allocated to the animal house. In defiance of hospital planning, the X-ray department was so embedded within the building that expansion was well nigh impossible. A derisory amount of space was allocated for radioisotopes. A trivial 32 beds had been allocated to mental illness, and there was still no sign of a department and chair in psychiatry being created. But the most dismaying feature was the ludicrous amount of space allocated for research in relation to bed space. The design gave every appearance of there having been a battle for beds between heads of departments.

Other points which he made were: quiet rooms in the noisiest part of the building, the sluice room farthest from the beds most needing its services and unrelated to treatment suite, cross-infection risks increased by infected material being brought into the ward suite for disposal and by inadequate air-conditioning, lavatories concentrated in blocks and not related to bed areas or day spaces, an operating-theatre with a wood-block floor which could never be sluiced clean, eight-storey light wells which meant that wards would be badly lit and have a wretched outlook.

All these blunders and many more, he added, would be housed in a dull cliff-like bulk of buildings unmistakably institutional in appearance.

Miss EDITH PITT, the parliamentary secretary to the Ministry of Health, welcomed the opportunity of discussing the University Hospital of Wales and of replying to some of the criticisms. The fact that it was an undergraduate medical school dictated not only the concept of the work to be performed there but also the site of the hospital, which was to have 650 beds. The scheme must be viewed against the development of acute hospital services in South Wales, which included not only another major acute regional hospital working in the Cardiff area but also major acute hospitals at Bridgend, Pontypridd, and Newport, and others in the Welsh Hospital Board's plans for Merthyr and North Monmouthshire.

The Board of Governors of the United Cardiff Hospitals and the Welsh National School of Medicine desired a hospital integrated with a medical school, with the closest possible working arrangements between the professional and the clinical staff and with the various departments and their research and other laboratories. An architectural competition for an important scheme of this size was thought preferable to selecting an architect, because it was believed that competition would give incentive to a number of architects to think about the problems set by the promoters and that new ideas and techniques might be evolved. Competition, however, could do no more than select an architect and, in a scheme of this size, a fundamental design. The promoters and architect could deal with each other on paper only in broad outline. The details must wait till later. A series of working parties had now been set up to go into the plans of the various units with the architect and with the engineer.

Ward units, outpatient department, lifts and communications, catering and food distribution, training accommodation, the dental school, were all being looked at in this way. The internal design and layout of the ward unit, for instance, had already been replanned to provide better access and better supervision to take account of the latest thoughts on cross-infection, more single rooms had been provided, and the large ten-bed unit had been broken up into smaller units.

This was a normal process which one would expect to take place with any design and similar replanning was going on throughout the hospital. The promoters had examined the design carefully in the light of the numerous criticisms and were satisfied that the completion of the process of preparation of detailed sketch plans, which was now going on, would give them a modern and efficient hospital and a medical teaching centre. She thought it premature at this stage to be too critical of the detailed planning because the details had still to be filled in. It was her earnest hope that, when this hospital was completed, the Welsh people would have a hospital in accordance with their wishes and a hospital of which they might be proud.

QUESTION TIME

Poliomyelitis Vaccination

At Sept. 30, 13,333,000 people in England and Wales had been vaccinated against poliomyelitis under the National Health Service.

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* Details of these proposals are given on p. 1081.
† Details of these proposals are given on p. 1082.

Appointments

BIRKBECK, M. Q., M.B. Cantab., D.PHYS.MED.: consultant in physical medicine, Northampton-Kettering area.

BROWNE, M. P., M.B.E., M.B. N.U.I., D.T.M. & H.: airport M.O., health control unit, London Airport.

BURTLES, RICHARD, M.B. Lond., F.F.A. R.C.S.: consultant anæsthetist, Northampton and Kettering area.

EMERY, RALPH, M.B. Lond., M.R.C.P.E., D.P.M.: assistant psychiatrist (S.H.M.O.), Aylesbury and High Wycombe area.

ETON, BRUCE, M.D. Manc., M.R.C.O.G.: S.H.M.O., maternity hospital, Cambridge.

LUNN, J. E., M.B. Glasg., D.P.H., D.P.A.: assistant M.O.H. and assistant school M.O., Oldham.

ORTON, W. T., M.B. Belf., D.P.H.: senior assistant M.O., Wembley and Willesden.

Birmingham Regional Hospital Board

BATTEN, R. L., F.R.C.S.: consultant surgeon, West Bromwich group of hospitals.

GALLA, THOMAS, M.B. Edin., D.P.M.: consultant and deputy medical superintendent, St. Edward's Hospital, Cheddleton and Stoke-on-Trent hospital group.

HILL, EILEEN E., M.D. Glasg., M.R.C.P., D.C.H.: consultant pædiatrician, Birmingham (Selly Oak) hospital group.

ROBB, H. P., M.B. Aberd., D.P.M.: consultant psychiatrist and deputy medical superintendent, Lea Hospital and Lea Castle Hospital.

ROSS, J. H., M.D. Cantab., M.R.C.P., D.OBST.: part-time consultant physician, Herefordshire hospital group.

SAGE, R. H., M.B. Birm., F.R.C.S.: consultant surgeon, Birmingham (Selly Oak) hospital group.

Liverpool Regional Hospital Board

OSWALD, D. C., M.B. Dubl.: assistant pathologist, Birkenhead H.M.C.

PORTER, R. A., M.B. Belf.: deputy medical superintendent (S.H.M.O.), Moss Side Hospital.

SNOW, R. G., M.B. Birm., F.F.A. R.C.S.: part-time consultant anæsthetist, Chester area.

Manchester Regional Hospital Board

FLEMING, A. C., M.B. Durh., D.P.M.: consultant psychiatrist and medical superintendent, Calderstones Hospital, Whalley, near Blackburn.

GRIMSHAW, LINTON, D.F.C., M.B. Manc., D.P.M.: consultant psychiatrist, Bury and Rossendale hospital group.

KRAWIECKI, J. A., M.B. Edin., D.P.M.: consultant psychiatrist, West Manchester and Springfield and Swinton hospital group.

METCALFE, W. J., M.B. Manc., F.R.C.S.: consultant surgeon, Blackburn and district hospital group.

SIMPSON, D. C., M.B. Edin.: senior casualty officer, Withington Hospital, near Manchester.

Obituary

JAMES ERIC PATERSON

M B Glasg , F R F P S

Mr J E Paterson, honorary consultant in neurosurgery to the Scottish Western Regional Hospital Board, died at his home in Rothesay on Oct 26

He was the son of a doctor and graduated from Glasgow University in 1911 as the most distinguished student of his year He spent some years in resident hospital posts, in general practice, and in junior staff appointments in surgery, gynæcology, and anæsthetics before he joined the R A M C to serve in France during the first world war After the war he returned to general practice and part-time specialism, and in 1920 was elected F R F P S

In 1926 he was offered the post of visiting surgeon to Stobhill Hospital, Glasgow, at that time a poor-law institution with 2000 beds for the aged and the chronic sick This appointment required him to give up general practice but gave him no chance to build up a consulting practice, and its acceptance meant a considerable financial loss A colleague relates

" To be poorly paid for tending the ' dregs of humanity ' was no deterrent to this extraordinary little man From the apparent dross he extracted much gold and gained a breadth of experience which few have achieved To suit his poor-risk patients he developed multi-stage operations He quickly learned the need for meticulous preoperative preparation and postoperative care and set up a specialised anæsthetic service In the early '30s his was a lone voice preaching the gospel of biochemistry, and he used the, then, slight resources of that science to the full Blood-transfusions were commonplace in his work when they were seldom thought of elsewhere, and before the late war there was a blood-bank in Stobhill

" He was indeed a general surgeon, whose work ranged from the newborn to the geriatric patient and embraced all specialties His technique was superb Watching him operate was like turning the pages of a beautifully illustrated atlas of operative surgery The neat, the precise, the anatomical attracted him, and he derived much pleasure from his practice of abdominal and reconstructive surgery and from urology, but neurosurgery became his true love This specialty he developed step by step from zero, beginning with attempts to relieve the hopeless cases admitted to Stobhill for terminal care In less than ten years he changed his wards from what was derisively called the ' deid hoose ' to a teaching unit "

The worth of Paterson's work in neurosurgery was soon recognised, and he was appointed neurosurgeon to the Victoria Infirmary He continued to work there until the establishment of the neurosurgical unit at Hillearn in 1940 When the National Health Service was started, he gave up general surgery—not without much heart-searching—and confined himself to neurosurgery

E A T , once one of his students, writes

" Two things were noteworthy about Eric Paterson The first was that he was a great man With the cultivation of a new specialty he combined modesty, enthusiasm, unmitigated frankness about himself even more than about others, unvarying truthfulness, and an uncanny habit of being right in his judgments These are not the qualities which produce an overblown reputation during a man's lifetime, but they indicate the second noteworthy feature about him, which was that his greatness was not as widely known as might have been expected Instead he built a solid foundation of friendship, respect, and those ultimates in admiration—emulation and imitation He threw away opportunities to be grandiose, he gave limelight to juniors, and he demanded no ceremony Such attributes are looked back on after years with love Even his faults were venial, for though his irascibility towards foolishness was legendary he was never hurtful His influence will outlast more brittle reputations Nor for generations will the personal magnetism of the man fade from the minds of his pupils, and his pupils' pupils for even longer the traditions of the units they serve must reflect the imprint of his character "

S A sends a physician's tribute

" Wee Pat was really known and understood by only the surgeons This was entirely proper He belonged to them Maybe physicians—second to none in their admiration for him —like to imagine this frail little man cast in a different role To them it seemed strange that a surgeon should flit through the world on tiptoe—eager, tireless, and radiant His face—specs and all—was a classic for the students sensitive to the physiognomy of intellect Few men revealed in their demeanour, voice, and gesture so vivid a spectrum of human emotions the tranquillity of deep meditation, the turbulence of the exploring mind, the flash of anger, and the smoulder of despair But most memorable of all was his dazzling smile—impish and mischievous—transforming the senior surgeon into a jubilant schoolboy, but eloquent too of his deep humanity James Eric was splendidly endowed with the attributes shared by the artist and the philosopher-surgeon he was in love with the world of beauty; and its glory and splendour were reflected in his imagination Out of these his riches he gave abundantly to patient and colleague alike they rejoice in his talents, they grew and were fortified by his example "

W G also writes of the man as well as of the surgeon

" Wee Pat's knowledge of surgical literature was immense, but surgery by no means filled his life He regarded the world with childlike wonder so that all things were of interest to him In literature, poetry, biography, music, and philosophy he was astonishingly well informed Botany and geology were his delight Sailing was a pleasure with him till it became too strenuous for his years, and then he turned to painting Critical as he was of his own efforts here, he developed his not inconsiderable talents to the full by his customary intense application Because of all his interests he was self-contained, and boredom was unknown to him, but he loved to meet a fellow enthusiast and made many friends through his hobbies

" In his earlier years his sensitivity and his enthusiasm made him a little prickly and intolerant, but the passage of time wore away the sharp edges and left a benign, mature personality as stimulating as ever He had no ambition to order other people's lives, and as a committee man he was a self-confessed failure He could not tolerate scheming and lobbying

" When he retired many groups of friends and associates gave him dinners and presentations The Wee Man was deeply touched and quite bewildered by these tokens His modesty had never allowed him to guess his own greatness nor to realise that he had gained ' that which should accompany old age, as honour, love, obedience, troops of friends ' "

Mr Paterson leaves a widow and two sons, one of whom is in general practice at Forres

Mr C W KIMBELL

G C S writes

" It was in the unpleasant circumstances of the 1940 campaign and then in captivity that Kim's sterling quality of character showed itself in all its brilliant clarity His devoted care of the wounded prisoners and his unswerving loyalty to those who served with him were an inspiration to all Small wonder that he had a host of friends who remember with affection and admiration his generosity and kindliness and his inimitable conspiratorial chuckle To all those the world is now a colder place "

Notes and News

WORLD HEALTH ORGANISATION

AT a meeting in Geneva of the W H O Executive Board, which opened on Oct 25,[1] Dr V Butrov (U S S R) stated that the U S S R would give 2 million roubles in 1961, in addition to its previous contribution, to the malaria eradication special account The Board decided to recommend to the next World Health Assembly that part of the cost of the malaria eradication programme should be financed from the regular budget The Board recommended a supplementary budget for 1961 of $800,000 This includes $100,000 for W H O assistance to the Congo, a further $2,700,000 for the same purpose will be provided by the United Nations

The Board commended Dr M G Candau, the Director General of W H O , for the promptness and efficiency of W H O assistance, and requested that it should continue They also thanked the International Committee of the Red Cross, the League of Red Cross Societies, and Governments which had helped with the emergency health programme

MENTAL ILLNESS IN SCOTLAND

AT the end of 1959[2] the total number of people in Scotland who were under care for mental illness was 20,682 (467 fewer than at the end of 1958) Of those in mental hospitals (including the State Mental Hospital at Carstairs) 14,022 were certified patients (922 fewer than at the end of 1958) and 6385 were voluntary patients (472 more than at the end of 1958) The number of admissions (excluding transfers) during 1959 was 12,428 (990 more than in 1958) Admissions of voluntary patients increased by 1175 to 9977 (80% of the total), but admissions of certified patients dropped by 188 to 2451 8719 voluntary patients (1095 more than in 1958) left hospital during the year Discharges of certified patients (including discharges " by escape ") numbered 1935 (118 more than in 1958) of whom about two-thirds were classified as ' recovered "

At the end of 1959, the total number of certified mental defectives was 8421 (98 more than at the end of 1958) Of these 5107 were in institutions and 2466 under guardianship Admissions of certified defectives to institutions during 1959 numbered 445 (53 more than in 1958) 234 patients were also admitted on an informal basis and 29 patients were transferred from certified to informal status The number placed under guardianship was 111 (8 fewer than in 1958) 215 were discharged from compulsory detention (including those discharged " by escape ")

A special study of readmissions during 1959 showed that of all admissions during the year 4480 (36%) were of patients with a previous admission 1139 were readmitted within three months of last discharge, 886 (7%) within six months, 624 within nine months, and 365 within a year

A NOVEL CLINICAL TRIAL

THE ethics of clinical trials can raise heated discussions wherever doctors meet, whether in lecture hall, laboratory, operating-theatre, hospital common-room, or students' hostel Now, perhaps because his pseudonym covers a man with an F R.C S , Mr John Rowan Wilson has made a medical version of the dilemma of means and ends the centre of his novel, *Double Blind*[3]

A young bacteriologist is carrying out on a tropical island a double-blind trial with a vaccine against a form of encephalitis The trial is being financed by a German drug firm which hopes to patent part of the manufacturing process The island is an isolated primitive community under the tutelage of the Colonial Office In obtaining permission to carry out the trial in its hospitals and clinics official channels have been by-passed Though the natives normally give their permission before receiving the vaccine, it is unlikely that they realise the significance of the request On the other hand, " South Atlantic " encephalitis is an endemic and dangerous infection and its control would be an enormous benefit to the community Two deaths occur which may or may not be due to the vaccine A Catholic priest complains The Colonial Office, uneasily aware of lapses in protocol, if not in morality, send out a doctor to report on the trial

This complex epidemiological situation contains many of the important issues which beset the conscience of the research worker It is further complicated by the tense personal relations of the doctor, the bacteriologist, and his wife Their personal problems are solved by the novelist's manipulation of the plot The questions of general principle inevitably remain unsolved, but it is to their intelligent presentation that the book owes much of its unusual interest

BIOLOGICAL ENGINEERING SOCIETY

THE first scientific meeting of this society was held on Oct 15 at the National Institute for Medical Research, Mill Hill In his opening address, Sir Charles Harington drew a parallel between the state of biological engineering today and biochemistry half a century ago Perhaps in the years to come, he said, a fusion of the two disciplines of biology and engineering might result in biological engineering becoming as acceptable as biochemistry today In the meantime, advances in biological and medical science depended greatly on advances in engineering and instrumentation, and the society was making a valuable contribution by enabling biologists and engineers to work more closely together Prof R F Woolmer, the president of the society, thought it appropriate that this first meeting should be held at the Institute, for its work and organisation was a good example of the way in which engineers could work together with biologists About 100 people attended the meeting, and the programme of demonstrations was planned to give a cross-section of the subjects which the society hopes to cover

SPASTIC SCHOOL-LEAVERS

ONE of the most useful qualities of voluntary organisations is their refusal to leave fairly well alone The British Council for the Welfare of Spastics, now that they are satisfied that there is no longer a general shortage of school places for spastics, have turned their attention to the difficulties which these young people face when they go out into the world[1] A pilot survey made by the council gives a depressing picture

> Of 34 recent school-leavers only 9 were thought to be capable of becoming fully self-supporting Though 7 of these were in work only 3 were in jobs with reasonable prospects None had received any training Another group of 16 were described as ' doubtfully employable , and of these 5 were in jobs and 5 awaiting training None are ever likely to become financially independent The remaining 9 were expected to be unemployable

Thus, in all, only 12 were employed and not in very satisfactory jobs The highest wage earned was £5 10s , and even those of average intelligence were doing work well below their capabilities Of the 22 who are not in jobs some are in institutions or awaiting admission Others live at home and some attend occupation centres Some are waiting for training All are thoroughly under-occupied and lack enough interests to fill their days, and this leads to mental and physical deterioration In or out of jobs, they seem to lack friends and social life Clubs for the handicapped do not attract them, for whether practicable or not, they want to go out to work like other youngsters They seem to lack realism about their capabilities and of standards in the outside world, perhaps because of the inevitably sheltered atmosphere of the schools in which they were educated

The numbers in the survey are small, and the Council offer the results not as a basis for recommendations but as evidence of need. The results are a salutary reminder that, like the rest of us, the handicapped are living longer and that the support we give them must be continuous and flexible, keeping pace with their changing ages and circumstances

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[1] See *Lancet* Nov 5, 1960, p 1037

[2] Report of General Board of Control for Scotland for the year 1959 H M Stationery Office Cmnd 1160 1960 Pp 33 2*s* 6*d*

[3] The Double Blind JOHN ROWAN WILSON London Collins 1960 Pp 256 16*s*

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[1] Annual report 1959-60 The address of the Council is 13, Suffolk Street, Haymarket London S W 1

University of Cambridge

On Oct 29 the following degrees were conferred

M D—P A J Ball J H Cule, P C Gautier Smith, J C Kelsey, C G Rob (by proxy), David Wise
M B—T J Willis

University of Birmingham

Dr R L Edwards has been appointed senior lecturer and first assistant in the department of obstetrics and gynæcology

University of Glasgow

On Nov 5 the degree of M D was conferred on William Cullen (with commendation) and on Joseph Sluglett

University of Queensland

Dr T J Rendle-Short, lecturer in child health in the University of Sheffield, has been appointed to the newly established chair of child health in this university

Royal College of Physicians of London

Dr K D Keele will give the FitzPatrick lectures on Tuesday, Nov 29, and Thursday, Dec 1, at 5 P M, at the college, Pall Mall East, S W 1 His subject will be Evolution of Clinical Methods in Medicine

Royal College of Physicians of Edinburgh

A meeting of college was held on Nov 1, with Dr A Rae Gilchrist, the president, in the chair

A Hill Pattison-Struthers bursary for 1960 has been awarded to Dr Philip Lanzkowsky and the Jean Hunter prize for 1960 to Dr A W E Soysa

The following were elected to the fellowship

Eric James M M Whittet, Keshavarao Krishnarao Datey, H G H Richards, H R L Fraser, A B Hegarty, J S Robson, J A Loraine, Tadepalli Shamsunder Row, R C Jackson, Velva Schrire Agnes L Scott, B C Sinclair-Smith, A C Kennedy, John Butler, K L Stuart, Arthur Jarrett A R Somner D S Nand, S L A Manuwa, J H Hutchison, D F Cappell, J H Walters, K W Donald, A W Woodruff, Eric Samuel

The following were elected to the membership

C W Kidd, A P Meiklejohn, R M Vanreenen, Krishna Rao Purohit, H L Davis R W McConnachie, Thambippillai Vamadevan, A R Adams, N R Young William McQuaker Sean O Reilly, L H Harris D G B Powell, David Jacobson, Elaine M Belton, Ralph Emery, J K Binns, Sheikh Muhammad Haneef, Ram Singh, G C Timbury, Joseph Gatt Barry Lewis, Anand Mohan Sur, R G B Williamson, Hamdy Mahmoud El-Sayed, Samir Mohamed Omar Hilal, Mookencherry Cherian Mathews, A I Rae Frank Tsu Chang Hu David Burrows, Nedumchalil Markose Mathai Baboobhai Rambhai Patel B S David Achyut Govind Motiwale, Peter Taylor, N P Burns, Kishin Hingorani, J D Woolridge, Boon-Kheng Khoo, I R Lawson Pandramajal Narayanappa Krishnamurthy Khalid Haji Aboo Mitha Nalkundad Kyathappanavara Channappa, R A Osborn, Dona Priyalatha Wijesinghe, M D Bowie, Lotfy Labib Basta, Vishnukumar Gupta Erasmus Lynghdoh, M G Dunnigan, Iain Michie, Harischandra Ranasinghe, Ekpo Edet Eyo, Chenniah Javaraya Bhakta Ram, Krishnadhan Datta, Susil Chandra Munsi Subrata Sen, Cheruveetil Kochukutty Gopi Mohammad Ata, J A Waddell, Bhim Sen Ghisaram Singhal, Chandidas Gupta, Joseph Levin, E S Garnett, Gulamabbas Juma Ebrahim, W H S George, J A McBride

Heberden Society

Dr J J Bunim will give a Heberden oration on Friday, Dec 2, at 4 15 P M, at the Wellcome Foundation, Euston Road, London, N W 1 His subject will be a Broadened Spectrum of Sjögren's Syndrome and its Pathogenetic Implications

North West Metropolitan Regional Hospital Board

Lord Moynihan has been appointed chairman of this board

Albert Lasker Grants

The American Public Health Association have awarded grants to Dr F H C Crick, of Cambridge, and Dr M H F Wilkins, of London, for their work on processes governing heredity in living cells and viruses, and to Prof Lionel Penrose for his contribution to the development of human genetics and his findings on the effect of nuclear and other radiation on human beings and their offspring

On Wednesday, Nov 16, at 5 15 P M, at the Royal Free Hospital, Gray s Inn Road, London, W C 1, Sir William Morrow, physician to the Royal Prince Alfred Hospital, Sydney, will speak on ulcerative colitis

Applications are invited for grants for research into diabetes mellitus and associated diseases Further particulars may be had from the secretary of the research grants committee of the Association, 152, Harley Street, London, W 1

Diary of the Week

NOV 13 TO 19

Monday 14th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W 12
4 P M Dr Brian Ackner Depressive Illness—Clinical Syndrome and Treatment
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 P M Dr P D Samman Eccrine and Apocrine Glands in Health and Disease

Tuesday, 15th

UNIVERSITY COLLEGE, Gower Street, W C 1
5 30 P M Prof J H Gaddum Pharmacological Analysis of Tissue Extracts
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Dr K S Kirby Nucleic Acids and Cancer
INSTITUTE OF OBSTETRICS
3 P M (Hammersmith Hospital) Dr Helen Payling Wright Varicose Veins in Pregnancy
ST MARY S HOSPITAL MEDICAL SCHOOL W 2
5 P M (Wright Fleming Institute) Prof Norman Morris Human Relations in Obstetrics
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Mr G C Knight Trigeminal neuralgia
ROYAL ARMY MEDICAL COLLEGE, Millbank, S W 1
5 P M Dr Wilson, F INST P Nuclear Physics
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M (General Infirmary at Leeds) Dr Bertram Selverstone (Boston) Modern Treatment of Gliomas
MANCHESTER MEDICAL SOCIETY
4 30 P M (Medical School, University of Manchester) *Medicine* Dr J J Bunim (Bethesda) Alkaptonuria and Ochronosis

Wednesday, 16th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Dr A L Greenbaum Fat Metabolism
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Clefts, Vesicles, and Bullæ
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P M Dr J N Pattinson Abnormalities of the Mediastinum
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W 1
8 15 P M *General Practice* Dr G I Watson, Dr Samuel Leff, Prof C H Stuart Harris Infectious Diseases Today
HARVEIAN SOCIETY
8 15 P M (Joint meeting with the Osler Club at 11, Chandos Street W 1) Dr A White Franklin, Dr Maurice Long, Dr T F Cotton, Sir Geoffrey Keynes, Mr A Dickson Wright Harvey and Osler
UNIVERSITY OF LEEDS
5 P M (General Infirmary at Leeds) Mr G W Theobald Gynæcological Pain
6 P M Mr J B Farquhar Third State of Labour

Thursday, 17th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P M Prof D V Hubble The Endocrine Orchestra (Langdon Brown lecture)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Dr J C Kendrew The Structure of Proteins
BRITISH INSTITUTE OF RADIOLOGY, 32 Welbeck Street W 1
8 P M Mr J B Massey Mrs J J Gough Dr Walter Shanks Dr A M Jelliffe Role of Moving Field Techniques in Treatment with High Energy Radiation
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield Morris Orthopædic Hospital, Oxford
8 30 P M Mr J Crawford Adams Ischio Femoral Arthrodesis for Osteoarthritis and Tuberculous Arthritis of the Hip
MANCHESTER MEDICAL SOCIETY
8 P M Sir Robert Macintosh A Trip to Russia and China
HONYMAN GILLESPIE LECTURE
5 P M (University New Buildings, Teviot Place, Edinburgh) Prof T N A Jeffcoate Functional Disorders of the Female Bladder and Urethra
UNIVERSITY OF ST ANDREWS
5 P M (Physiology Department, Queen s College Dundee) Mr L N Pyrah Use of the Loops of Small and Large Intestine in Urological Surgery

Friday, 18th

UNIVERSITY OF LONDON
5 30 P M (University College) Prof M Westergaard (Copenhagen) Some Fundamental Concepts and Problems in Molecular Genetics
ROYAL SOCIETY OF MEDICINE
5 30 P M *Epidemiology and Preventive Medicine* Dr E R Hargreaves Epidemiological Studies in Cornwall
ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION
2 15 P M (1 Wimpole Street, W 1) Dr Eliot Slater *Hysteria 311* (Maudsley lecture)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A M Mr H Osmond Clarke Cervical Disc Lesions
4 P M Prof C E Dent Primary Hyperparathyroidism
FACULTY OF RADIOLOGISTS 47 Lincoln's Inn Fields, W C 2
4 30 P M Prof R W Scarff Prognosis in Carcinoma of the Breast (Skinner lecture)
PLYMOUTH MEDICAL SOCIETY
8 30 P M (North Friary House) *Dr Richard Asher See How They Come*

Saturday, 19th

COLLEGE OF GENERAL PRACTITIONERS
11 30 A M (B M A House W C 1) Dr Lindsey Batten The Medical Adviser (James Mackenzie lecture)

The Lancet · Saturday 19 November 1960

DISEASES OF THE BASAL GANGLIA

THEIR RELATION TO DISORDERS OF MOVEMENT*

D. DENNY-BROWN
O.B.E., M.D. N.Z., D.Phil. Oxon., LL.D. (hon.), F.R.C.P.
PUTNAM PROFESSOR OF NEUROLOGY,
HARVARD MEDICAL SCHOOL, BOSTON, MASS.

I

THE term basal ganglia has no precise limitation, having been used by the older anatomists for the large grey masses at the base of the brain, including the optic thalamus. In the present century the thalamus has been excluded, and the use of term limited to the caudate nucleus, the putamen, and the globus pallidus. For neuropathological reasons certain closely related subthalamic nuclei are often included. I shall not here discuss the intricate, and in part disputed, interconnection between these structures. The most important of these are shown diagrammatically in fig. 1, which is designed to emphasise the reflex pathway from the intralaminar (I.L.) and centrum medianum (C.M.) nuclei of the thalamus to the globus pallidus, putamen, and caudate nucleus, and the efferent connections of these nuclei with the subthalamic nucleus (S.), the reticular formation of the midbrain (M.B.R.), and the substantia nigra (S.N.). Short pathways connect these scattered subthalamic structures with the important motor reticular formation of the brain-stem. The caudate nucleus, putamen, and globus pallidus also receive pathways from various areas of cerebral cortex. The caudate nucleus contributes an important pathway to the lateral thalamus. Though the basal ganglia are closely interrelated with the cerebral cortex in this way, they preserve both structure and function in its absence. This independent reflex activity is responsible for much of the behaviour that distinguishes the decorticate from the decerebrate animal.

My first objective is to define the degree to which diseases affecting the different ganglia produce consistent physical signs. Before 1895 there was no hint that damage to this region of the brain had any specific effect, though in the time of Hughlings Jackson it was customary to regard the basal ganglia as the seat of regulation of those simple spasms that remain when the cerebral cortex is destroyed. The first hint that specific disorders of movement are related to limited disease of these ganglia appears to have been the excellent description of congenital double athetosis by Anton in 1896, with the related scarring of the outer putamen on both sides. The most convincing demonstration, however, was the description of progressive lenticular degeneration by Kinnier Wilson (1912), providing a dramatic demonstration of the relation of limited lesions of these ganglia to rigidity, distorted posture, and tremor. Only then did the earlier descriptions of outfall of nerve-cells in the globus pallidus in paralysis agitans by Jelgersma (1908), and the comparable atrophy of the caudate nucleus in Huntington's chorea described by Alzheimer (1911), assume real significance.

As had so often happened in relation to clinicophysiological correlation in cerebral disorders, the rush to stake out claims on the anatomical terra nova outran both the available physiological philosophy and the necessary neuropathological experience. Indeed the Croonian lectures of Kinnier Wilson (1925) are wholly devoted to a sobering criticism of the massive superstructure that had already burdened the topic. The difficulties that pervade the subject are derived from the very general nature of the pathological processes that affect these structures, the kaleidoscopic variations in resulting symptomatology, and the poorly understood part that the ganglia play in normal cerebral function.

Hepatolenticular Degeneration

The striking demonstration of lenticular cavitation in hepatolenticular degeneration (Wilson's disease), though important in other respects, was most misleading in its implication that the disease process was itself localised. The widespread nature of the gliosis that accompanies all forms of the disease (Hall 1921) is now generally recognised. That the disease is an inborn error of metabolism resulting in accumulations of protein-bound copper in many organs, particularly the liver and nervous system, is also well understood. Within the nervous system greatly increased concentrations of copper are present in the putamen and thalamus, and to a less extent in the cerebellum and cerebral cortex (Cumings 1948, Spillane et al. 1952, Cartwright et al. 1954). The striking improvement that can follow removal of small amounts of copper from the body by chelation indicates that, in some cases, a

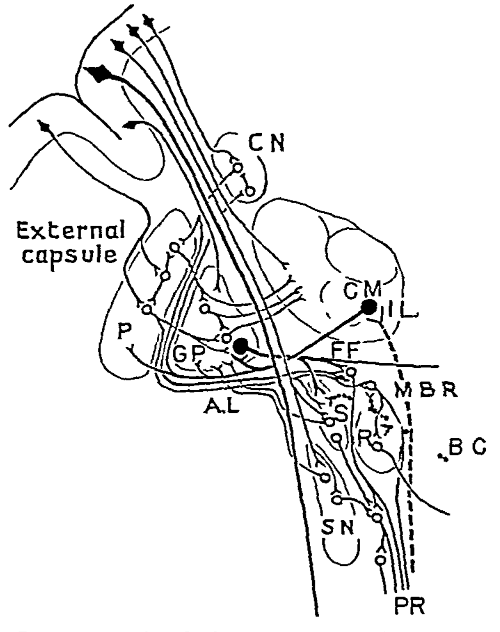

Fig. 1—Diagram of the chief connections of the basal ganglia.

The efferent systems of the globus pallidus (G.P.), putamen (P.), and caudate nucleus (C.N.) pass through the ansa lenticularis (A.L.) to the fields of Forel (F.F.). There they reach the subthalamic nucleus (S.), the scattered nuclei of the midbrain reticulum (M.B.R.), substantia nigra (S.N.), and red nucleus (R.), with connections to the reticular nuclei of the pons (P.R.). The reflex circuit has an afferent limb in the lemniscus and ascending tegmental tracts (represented as a broken line) through the intralaminar (I.L.) and central (C.M.) nuclei of the thalamus. The midbrain and subthalamic reticular nuclei receive terminations of the brachium conjunctivum (dotted line B.C.).

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* From the Croonian lectures for 1960, delivered before the Royal College of Physicians of London on Feb. 23 and 25.

relatively small fraction may in time interfere with vital enzyme function In the juvenile type such improvement is unfortunately offset by other unknown factors

When the symptoms start after the age of 20 the disorder appears as flapping tremors at the wrist and shoulders, which are absent at rest and provoked by movement The very diffuse gliosis of the nervous system that is then present makes it impossible to relate such incoordination to damage to any particular structure The tremor has some features in common with that caused by other types of damage to the midbrain reticulum The fate of such cases is usually determined by the severity of the associated hepatic cirrhosis If they survive for long a generalised mild muscular rigidity ultimately appears in all limbs, predominantly in flexion, in association with severe dysarthria and dementia There is then widespread fibrosis of the cortex, thalamus, and basal ganglia

In the juvenile types of Wilson's disease involuntary movements of a different kind occur These are at first small involuntary lapses in posture At or about the same time the natural facial expression changes, the mouth is held more constantly open, and the eyelids blink seldom The changes in expression, associated with slight postural changes in the hands in the nature of overextension of the fingers (fig 2*a*), long precede the dysarthria and facile smile that were noted by Wilson Gradually the postures of the limbs become more stiff—at first in walking, when they tend to overextension first on one side and then on the other—leading to an awkward clumsy gait A plastic rigidity is then apparent in the affected limbs It is at this time that a slurred dysarthria is usually first noticed As the disorder progresses first one then the other arm becomes flexed in a hemiplegic posture, and the lower limbs become more constantly extended As these postures develop, tremor usually appears In some patients the tremor is that of the adult type of the disease, a rapid alternating flapping at the wrist and fingers In others it begins as athetosis, with slow swings from overextension of the hand to overflexion In this type the swing of movement may in time accelerate and make gradual transition into a parkinsonian type of tremor In most patients the swings of athetoid movement become slowed by increasing rigidity, the hand becomes more continually flexed and the ankles overextended as part of the terminal hemiplegic dystonia that was illustrated so well in Wilson's original description

I should like to draw particular attention to the evolution of the terminal dystonic state in hemiplegic attitude, for this has, in my experience, been invariably present when bilateral rarefaction or frank cavitation of the putamen has occurred In time there is yet a further change in the symptomatology, in the nature of lessening of the hemiplegic rigidity, and its conversion into a state of mild general flexion (fig 2*b*), with flexed wrists and extended fingers and ankles If the patient is lifted from the bed, the limbs still stiffen, resuming in some degree the earlier rigid hemiplegic posture (fig 2*c*) I shall later return to the significance of these postures, for they are a key to much that is obscure in the pathophysiology of the basal ganglia

Huntington's Chorea

It is not necessary here to outline the characteristics of Huntington's chorea except to point out some distinctive

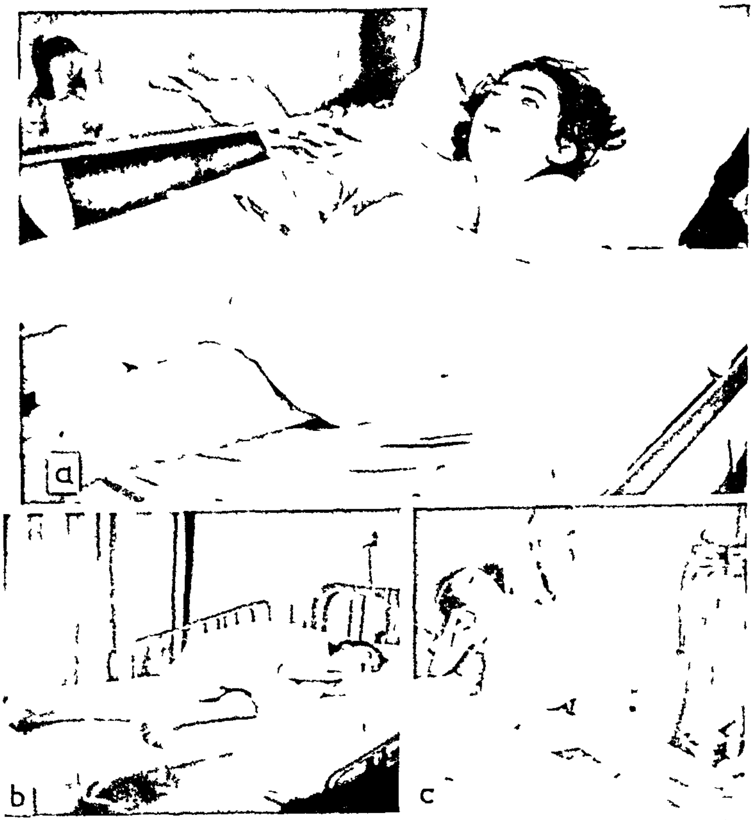

Fig 2—To show (*a*) the early abnormalities of posture in a patient of 16 beginning to show signs of hepatolenticular degeneration *In (b) is shown the posture of the* same patient 4 years later in an advanced stage of the disease (note the overflexed wrists with extended fingers) If the patient is lifted from contact with the surface of the bed (c) all limbs stiffen and the lower limbs extend

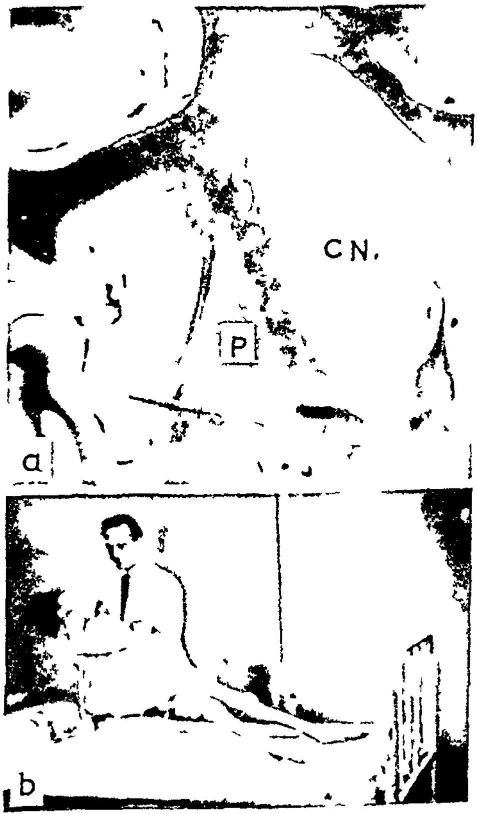

Fig 3—To show (*a*) the extreme atrophy of the caudate nucleus (C.N) and to a less degree of the middle third of the putamen (P) in an advanced stage of Huntington's chorea; and (*b*) the rigid posture when such a choreic patient is raised from the bed

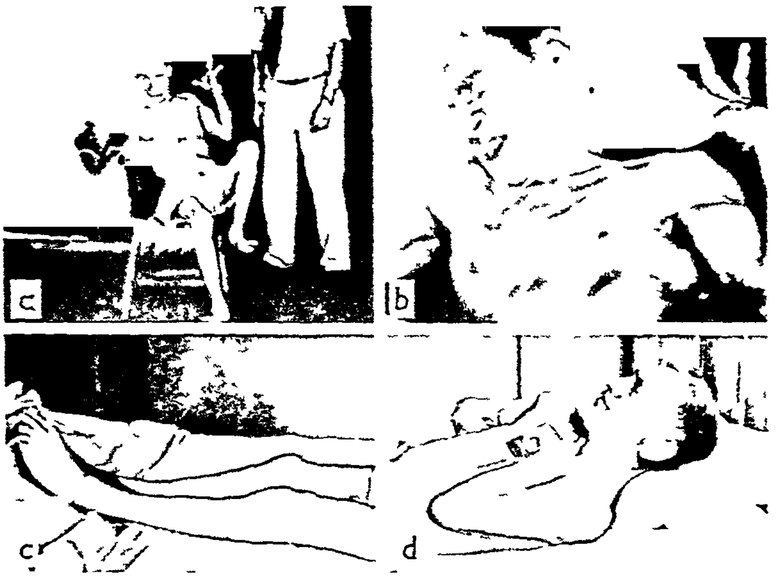

Fig 4—To show the "mobile spasm" with athetosis of hands and lips (*a* and *b*) in double athetosis. In the terminal stage a rigid posture of extension of the lower limbs (*c*) and flexion of the upper limbs (*d*) replaces the "mobile spasm"

features of the involuntary movements and postures. The movements are essentially labile and haphazard in distribution. I have described elsewhere (Denny-Brown 1950) how the movements of the hands and arms gradually assume the swings of posture seen in athetosis, though at a faster rate. This is first seen in walking. The movements of the lips and jaw gradually develop the wider amplitude, with associated incoordinate action of the platysma muscles, that is a feature of double athetosis. For a long time the limbs are hypotonic, but the posture gradually becomes more stooped, and in late stages of the disease rigidity may appear, with more characteristic slower athetoid movements. The posture is then a rigid hemiplegic attitude, which is greatly intensified by raising the patient from contact with any surface (fig 3). The arms are strongly flexed, and the legs and ankles stiffly extended. This posture is the same as that mentioned as a late stage of Wilson's disease.

When the onset is early, rigidity may be the most prominent symptom (Kehrer 1928). There is then close resemblance to parkinsonism, including pill-rolling tremor of the fingers (Fleischhacker 1924, Josephy 1936). In a few patients unmistakable parkinsonism develops later in life (Chandler et al. 1960) though the lower limbs are, in my experience, more often extended stiffly than flexed in the usual parkinsonian posture. Besides atrophy of the frontal cortex shrinkage of the caudate nuclei is almost universally present, together with some loss of cells in the middle third of the putamen (Marie and Lhermitte 1914, Dunlap 1927) with pallor of the corticostriate and striopallidal systems (fig 3). A condition of fibrous scarring of the putamen, called "status fibrosus" by the Vogts (1920) and Jakob (1923), has been found in the cases presenting rigidity (Bielschowsky 1919, Terplan 1924, Freund 1925). In some cases the degeneration extends to the globus pallidus and subthalamic nuclei. The extrapyramidal manifestations of Huntington's chorea, as with Wilson's disease, are seen to form a spectrum of types of movement disorder in relation to an evolving pathology, ranging from early myoclonic twitchings in some cases to torsion spasm and rigidity and, more rarely, parkinsonism. The most characteristic choreic movements reflect only the usual early affection of caudate nucleus and frontal cortex.

Double Athetosis

The case selected by Vogt (1911) as the prototype of striatal disease presented an unusually well-localised marbled scar in the outer segment of the putamen on both sides. The clinical symptoms are usually a bilateral labile type of athetosis affecting all parts, but particularly the hands, mouth, and neck, and present from the first year of life. The condition is now well recognised, and is usually called "double athetosis" (fig 4*a* and *b*). The scar tissue appears to be a static inactive process. Many follow Courville (1953) in attributing it to anoxia at birth. In several cases there has been similar scarring of the cerebral cortex (Alexander 1942), but there is no doubt that the lesion in the putamen can occur alone, and in association with a bilateral mobile type of athetosis present from soon after birth. In many cases rigidity of the limbs appears later, gradually slowing the athetosis to "mobile spasm" and leading ultimately to intense flexion of the upper limbs and extension of the lower limbs (fig 4*c* and *d*). When rigidity has complicated athetosis in this way the scarring of the putamen is usually more extensive, but few cases have been analysed from this point of view.

Dystonia Musculorum Deformans

In its progressive form, dystonia is the most striking and grotesque of all neurological disorders. The progressive small spasms of flexion of a lower limb, or alternatively of torticollis, that are usually the first manifestations in early childhood, first appear as additions to movements such as walking. Only when continuous maintenance of the abnormal posture occurs is the dystonic condition recognised. Though I have earlier indicated the essentially athetoid character of the beginning of the disorder (Denny-Brown 1945), its relation to athetosis is still overlooked, for the first signs are spasms in willed movement rather than involuntary movements. As the disorder progresses new intermittent elements of athetoid spasm make their appearance, they are set up, like the first, by any stimulation or attempted movement, but they gradually become more constant. The cumulative steady spasm of flexion of proximal joints has added to it extension of the fingers and toes, retraction of the jaw and lordosis. The later addition of intermittent spasm in antagonistic muscles followed by continued contraction in antagonists, leads to the great deformity. Unless there is accompanying spasticity, the asymmetrical postures and movements can be profoundly changed by altering the areas of body in contact with the bed or examining table. If the patient is lifted free from all contact with the body surface, save for support under the axilla, the upper limbs flex and the lower limbs extend in hemiplegic posture (fig 5). If movements have been in progress they cease when the child is suspended. When the patient lies on one side the lowermost limbs extend and the uppermost flex. These changes indicate that reflex effects from contact between the body and supporting surface are important factors in the production of the abnormal movements and postures

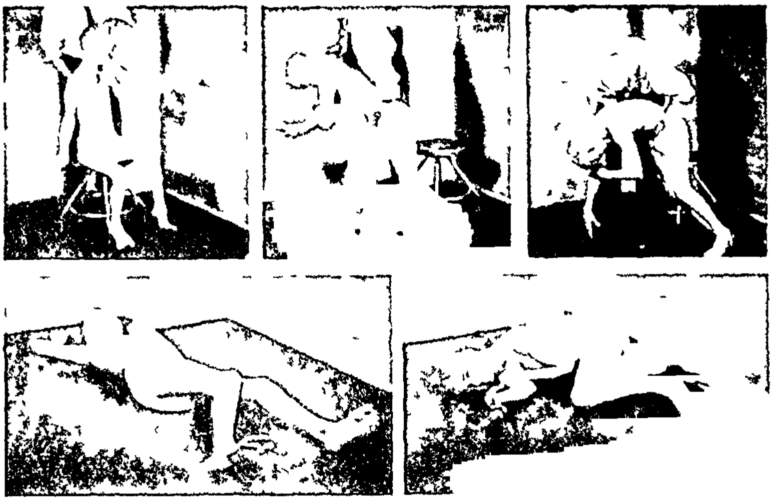

Fig 5—Dystonia musculorum deformans To show the abnormal attitudes and their modification by suspending the patient and by lying on a flat surface
(Photographed at Wrentham State School, with kind permission of Dr Carl Quinn)

Dystonia is a symptom complex that has many causes, but the irregular and grotesque progressive deformity described above, with cumulative development in one body part after another, has not been clearly correlated with pathological processes other than status marmoratus, which closely resembles the lesion of double athetosis, but usually involves the thalamus and cerebral cortex in addition to the putamen Thomalla (1918), Wimmer (1921), Jakob (1932), and others have reported the lesions of Wilson's disease in relation to relatively symmetrical dystonia Lethargic encephalitis was undoubtedly the cause of many cases of asymmetrical dystonia of partial and arrested types The cases of Cassirer (1929), Jakob (1923), Marinesco and Nicolesco (1929) and Laruelle and van Bogaert (1929) showed milder changes in the form of pallor of the globus pallidus and cell loss in the putamen There is some possibility that such cases are postencephalitic

More Diffuse Lesions of the Basal Ganglia

From the great variety of diffuse degenerative processes that affect the basal ganglia, I have singled out Wilson's disease, Huntington's chorea, and status marmoratus as examples where rigid " dystonic " states can be related to relatively localised destruction of the putamen Before turning to the problem of parkinsonism, we should briefly review some of the other types of diffuse pathology that affect the basal ganglia These are all rare and obscure syndromes, and I shall here only comment on the type of movement disorder in relation to anatomical lesion

Calcification of the basal ganglia (Fahr's syndrome) is an affection of the walls of small blood-vessels of these organs that may reach considerable intensity, even to the degree of visibility in skull X-rays (Fahr 1930), without neurological symptoms There may or may not be associated hypoparathyroidism (Sugar 1953) The neurological disorder that eventually appears is a generalised rigidity, most commonly beginning in the lower limbs (Fritsche 1935, Chavany et al 1949), with or without athetoid movements Parkinsonism developed in middle life in the patients of Jakob (1923) and of Alexander and Tucker (1949) The calcification in such cases begins on the border between the putamen and globus pallidus In a remarkable familial case of my colleague, Dr Paul Yakovlev, such calcification resulted in dysarthria with intense ridigity of all limbs in flexion

Similar flexion postures eventually result from diffuse *lipidosis* of the juvenile type (Sjogren 1931, Watson and Denny-Brown 1953) Similarly in the *Hallervorden-Spatz syndrome*, where deposits of iron-containing pigment accumulate in the globus pallidus, thalamus, substantia nigra, and dentate nuclei, there results a diffuse rigidity of the limbs in flexion, with or without athetosis It is also notable that, both in this syndrome and in lipidosis, there is a liability to sudden jerks of the limbs in flexion (myoclonus) as a prelude to the eventual postural change

The Enigma of Parkinsonism

The most common of extrapyramidal syndromes—parkinsonism—presents the most difficult problems in this whole group of diseases There is still no agreement as to the essential change in anatomical structure

The pallor of the ansa lenticularis and related efferent pathways of the pallidum, and the progressive loss of cells in the globus pallidus and, to a less extent, the striatum, described by Jelgersma (1908) and by Lewy (1913), have been found by many others (Lhermitte and Cornil 1921b, Bielschowsky 1922, Jakob 1923, Foix and Nicolesco 1925) In 1919 Tretiakoff drew attention to some loss of cells in the substantia nigra in paralysis agitans, as well as to the severe destruction of this nucleus in postencephalitic parkinsonism This feature of the disease has gained greater emphasis in the past twenty-five years (Hassler 1937a and b, Benda and Cobb 1942) Greenfield and Bosanquet (1953) have confirmed scattered cellular changes in the locus cœruleus of the pontine tegmentum, as well as in the substantia nigra, found earlier by Foix and Nicolesco, and by Hassler In his posthumous textbook on neuropathology, Greenfield (1958) states that the lesions in the globus pallidus, though constant and sometimes severe, are " essentially those of senility "

Our own pathological material in the Boston City Hospital consists of 21 cases, 5 of them are clearly postencephalitic, 7 have atherosclerotic lacunar lesions in the putamen, and 9 could be clearly calssified clinically and pathologically as idiopathic paralysis agitans Only 2 cases had been subjected to serial whole-brain sections, but multiple sections of the basal ganglia and midbrain of all the others were available for study

All cases of parkinsonism exhibited some degree of pallor of the globus pallidus and the ansa lenticularis, in sections stained for myelin sheaths The corresponding loss of nerve-fibres was more impressive than loss of nerve-cells In *paralysis agitans* the pallor was usually uneven, and foci of loss or thinning of myelin sheaths were particularly evident in the outer pallidum near the external lamina In Nissl sections such foci were represented by small inconspicuous areas of loss of cells from the otherwise evenly scattered pattern of pallidal cells In 2 cases small concretions were present in the ground substance, not directly related to the foci Gliosis was mild in degree In no case was there any evident disease of blood-vessels, other than some mild siderosis in 2 cases (a change commonly found in the globus pallidus after middle life) In one patient who died after a head injury all striopallidal and corticopallidal fibres stained very poorly compared with the pallidal efferents in the ansa lenticularis In the most severely affected cases all the pallidal cells were shrunken and stained poorly, and their lipid content appeared to be increased in relation to their size In 5 cases, and doubtfully in 2 the substantia nigra showed the small lesions described by Hassler No cell or fibre lesion was found in the nigra in 2 cases

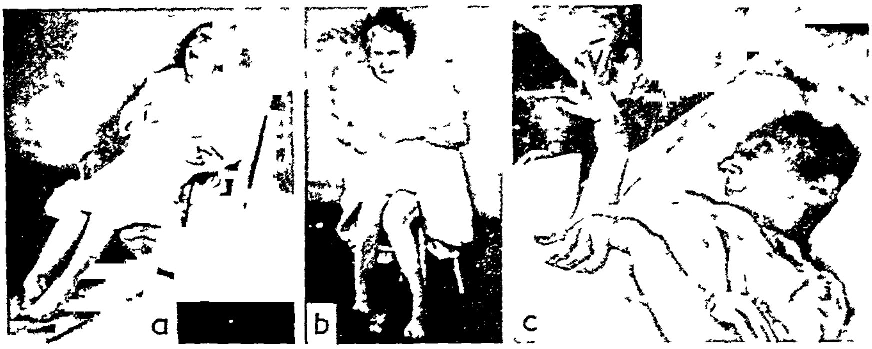

Fig 6—Terminal stages of paralysis agitans, to show flexion dystonia

The lesion of the globus pallidus is described by Bielschowsky (1922), and in detail by Foix and Nicolesco (1923, 1925), who called it "paravascular degeneration" It was regarded as the first stage of a change that later leads to more evident loss of tissue elements (*etat precrible*), and later still to pericapillary destruction of tissue (*etat criblé*) It should be emphasised, however, that in paralysis agitans with paravascular degeneration no evidence of change in the walls of blood-vessels can usually be found If siderosis is present it must be an independent abnormality, for it can be severe in degree without producing paravascular degeneration The pattern of tissue damage reflects some peculiarity in the permeability of the smallest blood-vessels in this area, and is common in the earliest stage of some of the metabolic diseases affecting the basal ganglia

When *atherosclerosis* has affected the vessels of the basal ganglia, lesions of the putamen are more obvious than those of the globus pallidus Lacunes of softening appear in the putamen surrounded by foci of *etat crible* The clinical state is then most commonly that of pseudobulbar paralysis, with or without damage to the internal capsule and cerebral white matter In 2 of our cases with typical parkinsonian tremor and attitude, mild *crible* lesions were limited to the internal part of the putamen and outer globus pallidus Only associated atherosclerosis of the arterioles, and the presence of the *crible* state in the putamen, then differentiate arteriosclerotic parkinsonism of this type from what we would call true paralysis agitans The pericapillary degeneration itself is more severe but otherwise closely resembles "paravascular degeneration" There may be small foci of similar paravascular degeneration in the substantia nigra, but these are not necessarily present Paravascular degeneration, I believe, is not directly the result of atherosclerosis but is worsened in extent and degree by its presence The evidence for this will presented elsewhere The occasional cell inclusions that have been noted by Lewy (1923), Hassler (1937a), and Greenfield and Bosanquet (1953) in the substantia nigra have been found in the Boston City Hospital in all types of case I am not convinced that they are a primary or specific change

In my monograph in 1945 I made a sharp distinction between true paralysis agitans and arteriosclerotic parkinsonism With greater experience I have to admit that this distinction is not absolute There is every degree of transition At one end of the scale one can recognise a slowly progressive gentle tremor at rest, with mild rigidity, that may begin in the fifth decade, with slight paravascular changes limited to the globus pallidus At the other extreme the marked rigidity and fixed hemiplegic posture of the pseudobulbar type is related to the "lacunar" state, with multiple small infarcts of the putamen Between lies every conceivable relative proportion of tremor and rigidity Thus arteriosclerotic parkinsonism may begin with rigidity, tonic grasp, and tonic foot response, with very little tremor In this type the putamen appears to be invariably damaged, and is perhaps first affected Yet rigidity can also occur with pallidal lesions A patient of mine, an 81-year-old man who had first developed typical parkinsonian rigidity and tremor twenty-one days before death, presented recent partial infarction (circumscribed pallor) of the globus pallidus on both sides There was no change in the substantia nigra Lhermitte and Cornil (1921a) cited a similar case

The symptomatology of paralysis agitans consists of the well-known tremor and rigidity In the tremor the opposed thumb beats against the first finger, and is associated with tremor of the lips and tongue before other parts The soft yielding plastic rigidity of paralysis agitans appears first in the flexors of the upper limbs, and is associated with delay in initiation of movement, though the relative degrees of bradykinesia and objective rigidity are greatly variable Seldom is it emphasised that in typical paralysis agitans the rigidity is invariably associated with change in posture, its preponderance in the flexor groups gradually leading to the stooped posture with flexed limbs, fixed facies with staring eyes, and open mouth, by which parkinsonism can be recognised in a photograph It is important also to emphasise that in the natural course of the disease the postural change gradually worsens until in a terminal stage all the limbs are drawn into a fixed attitude of general flexion (fig 6) The wrists are then strongly flexed and pronated, the fingers are extended, and the ankles are plantar flexed Attempted displacement of any part away from this attitude then meets a mounting resistance, and the part rapidly returns to its resting attitude This terminal loss of plasticity is associated with great lessening or loss of the tremor Speech is also lost or reduced to a mumble

Studies of arteriosclerotic parkinsonism indicate that the coarser the lesions of the external segment of the globus pallidus the more rapid has been the development of dystonia, with correspondingly less evident tremor If the putamen is involved tremor may not occur, and the rigidity is then not only more intense but also involves the extensors of the lower limbs and the flexors of the upper limbs (hemiplegic distribution) The pattern of rigidity as well as its intensity reflect the more lateral and lacunar lesions

In *postencephalitic parkinsonism*, though the same tremor may be present, it is more often damped or abolished by an intense asymmetrical rigidity The rigidity passes more rapidly into the fixed attitudes of dystonia, leading to torticollis, scoliosis, and grotesque postures of the limbs On the side on which dystonia was absent or delayed in appearance, the tremor tends to be more violent and more extensive than in paralysis agitans In addition various forced movements and compulsions, of which the oculogyric crises are the best known, are peculiar to the postencephalitic state Like others, we at Boston have found a severe destruction of the substantia nigra in all cases, but we have also found a diffuse pallor of the fibre systems of the globus pallidus Obvious nerve-cell changes in the globus pallidus or striatum are seldom found, but small foci of lesser change are common More important, we have often found loss of the small thinly medullated fibres entering the external putamen from the external capsule, and the external lamina of the globus pallidus from the internal capsule, with or without paucity of striopallidal fibres There is corresponding gliosis This inconspicuous change is of great significance in relation to the prominence of symptoms of corticostriate and corticopallidal disorder, and I shall return to it in my second lecture In the acute stages of lethargic encephalitis destruction of the substantia nigra was commonly found in patients without parkinsonism (Meyer 1923, Holzer 1926) If 75% of the substantia nigra is destroyed in most cases of postencephalitic parkinsonism, this still fails to account for the varied and complex disorders of motor function of that disease, and their delay in appearance Still less is the similar symptomatology in paralysis agitans explained by the inconstant meagre changes in the substantia nigra and locus cœruleus in that disease

Focal Lesions of the Basal Ganglia

The natural history of diseases that commonly affect the basal ganglia of the brain has been outlined in order to draw attention to their general tendency to produce involuntary movements that progress slowly to states of rigid maintenance of abnormal attitude We shall now turn to the effects of acute destructive lesions, which, by contrast, produce striking disorders of attitude from their beginning

Necrosis of the Striatum (Putamen and Caudate Nuclei)

Bilateral symmetrical necrosis of the caudate nucleus and putamen has been found in conditions such as death from status epilepticus in children, when anoxic damage to small vessels is presumably the primary mechanism

Marinesco and Draganesco (1929) describe this condition after convulsions in a child aged $4^1/_2$ years, who survived to the age of 6 There was patchy laminar necrosis of the cerebral cortex, and only mild degenerative changes were found in the globus pallidus Until death the child lay in an unresponsive state without making purposeful movements There was complete absence of speech, and swallowing was difficult At first the limbs were extremely rigid in flexion, but they would extend with changes in posture, and athetoid movements were present Later rigidity was less evident when the child lay on a surface, though all the limbs were semiflexed, the wrists pronated, the fingers flexed, the ankles extended, and the toes plantar flexed When the child was suspended in air, all the limbs became intensely rigid, the arms flexed, the hands clenched, the lower limbs extended, the ankles inverted, and the toes flexed This posture would persist as long as the child was suspended This phenomenon of the appearance of rigidity when the patient is lifted from a surface is commonly called ‘ the Foerster syndrome ” Foerster (1909), however, described only the atonic type of cerebrocerebellar diplegia, and the extension of the limbs when suspended appears to have been first described by Batten and von Wyss (1915)

Hawke and Donohue (1951) described, in a 13-year-old child, a similar complete bilateral necrosis of the whole corpus striatum, caudate, putamen, and globus pallidus, which occurred during a febrile illness complicating otitis media, without any known episode of anoxia During two months of survival the child did not speak or respond to commands The eyes would follow the movements of another person, and even moving objects late in the survival period The muscles were at first hypotonic, but they gradually became stiff in flexion, particularly during passive movement Occasional myoclonic twitching of muscles was observed The remarkable phenomenon of rigidity when suspended is not mentioned by these workers Similar cases have been reported by Verhaart (1938)

Complete clinical and anatomical studies of cases of unilateral destruction of the putamen and caudate nucleus are equally rare I cannot here discuss in detail such a case in the collection of my colleague Dr Yakovlev, suffice it to say that for the last ten years, before death at the age of 25, the patient had presented a dystonic contracture of the right arm in flexion and the right leg in extension, with consistent flexor plantar responses There was a severe spastic dysarthria Mobile athetoid spasm of the hand had preceded the dystonic attitude of extended fingers, and flexed wrist and elbow Steck (1921) reported a similar case, though the dystonia was not fully described

When bilateral partial cystic infarction of the putamen has occurred without damage to the internal capsule, the clinical condition has been that of pseudobulbar palsy (as first described by Richard Bright 1831) The pseudobulbar state resulting from Wilson's disease, and the condition resulting from manganese poisoning (Peñalver 1955, Berry and Bidwai 1959), have obvious features in common

Necrosis of the Globus Pallidus

One of the most striking lesions of the basal ganglia is the symmetrical necrosis of the globus pallidus found in patients who have had an episode of coma as a result of inhalation of coal gas, or carbon monoxide, or occasionally nitrous oxide, and rarely in those who have had other types of asphyxic anoxia It can also follow intoxication by carbon disulphide (Richter 1945)

The patient commonly recovers from the initial coma, and he may be discharged from hospital apparently completely relieved, or with only slight mental confusion After one to three weeks, he may then relapse into coma a second time, and succumb in that state Most often the delayed relapse presents as the onset of an akinetic mute state, with rigidity In other cases the relapse takes the form of renewed confusion in which elements of visual agnosia and catatonic postures are prominent, presumably resulting from lesions of cerebral white matter In a few cases a mild parkinsonian rigidity makes its appearance within six weeks of recovery from the initial coma

I need not here discuss the many interesting aspects of the neuropathology, which has recently been reviewed by Meyer (1958), whose earlier papers are among the most authoritative Widespread patchy areas of cortical ischæmic damage may occur Their presence is to be suspected whenever mental confusion is persistent The lesion that concerns us here more particularly is necrosis of the globus pallidus It is commonly found when death has occurred soon after exposure, without recovery from coma, and it is usually bilateral and approximately symmetrical Some part of the globus pallidus, usually the most anterior part of the internal segment, is the site of a hæmorrhagic softening, commonly occupying only a small part (10 to 20%) of the nucleus There is usually no incrustation of the vessels in this early stage The necrosis is clearly secondary to vascular damage

Where death has occurred after a delayed relapse, with onset of akinesia and rigidity, the infarct is usually larger, and it may involve the external segment or even portions of the putamen An associated lesion of the substantia nigra has been reported (Hiller 1924) but is very rarely found In a few such cases evidence of cortical damage is very slight, and white-matter lesions have been absent

Of 2 such cases followed closely in life, 1 showed an unvarying akinetic state for six months

This 58-year-old man was found in coma in a small unven-

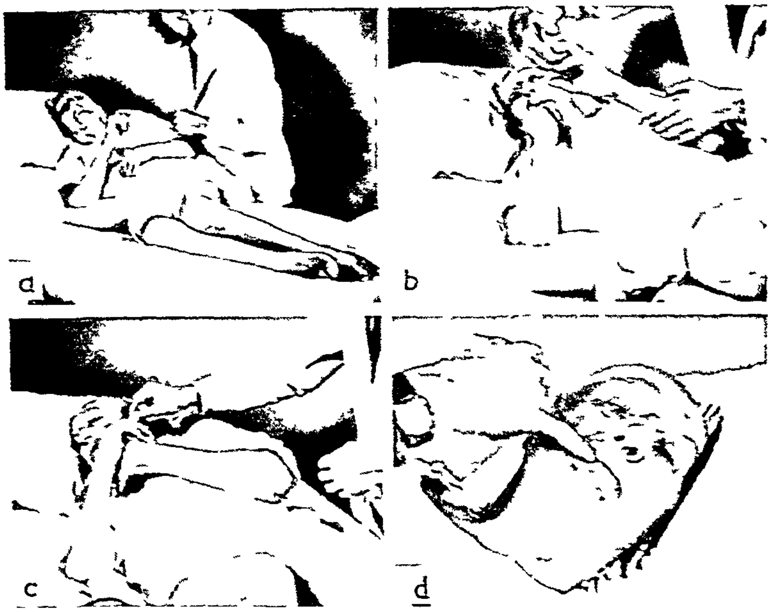

Fig. 7—Carbon-monoxide poisoning: (a) to show the flexed akinetic mute state, (b) the absence of grasp response, (c) the small response to pinprick on the face, and (d) tight closure of the mouth when lips were touched.

tilated hut, with a burnt-out brazier fire, without chimney. He lay unreflexic for a day but then made a rapid recovery. Eight days later he was able to speak, to read a newspaper, and to travel from Florida to Boston. On the ninth day he was found to be very drowsy, and he rapidly lapsed into an unresponsive state, with arms and legs moderately rigid in semiflexion. His eyes were open and they occasionally followed the movements of the examiner. He slowly scratched the face if pricked with a pin, but he gave no other reaction. The deep-tendon reflexes were present but not increased. Both plantar responses were extensor. The face was expressionless. Swallowing was possible only if fluid was introduced far back into the mouth. Any attempt to open the lips or mouth passively met increasing resistance. The limbs were held continuously in a semiflexed posture, the wrists were flexed, and the ankles extended. Because of mild plastic rigidity, they resisted attempts to extend them passively. The fingers were extended and were not used, except for a feeble brushing movement at a noxious stimulus to the face. There was no grasp response to a light stimulus, but, occasionally, after heavy stroking, a feeble grasp was obtained. Such responses are illustrated in fig. 7 from another patient who survived in an identical state for many months but in whom necropsy was not obtained.

In the first patient examination of the brain showed the characteristic lesions of the globus pallidus. There was no lesion of the substantia nigra, or thalamus, or other part of the extrapyramidal system. The cortex was virtually unaffected, but some patchy lesions in the frontal white matter of the orbital cortex were found on both sides, with a smaller lesion in the deep parietotemporal white matter. In this case vascular lesions of two different stages were apparent, supporting the hypothesis that the lesion had in fact enlarged after the latent interval. The occluded vessels were calcified in the area of more recent extension of softening.

In general small pallidal lesions have not been associated with extrapyramidal signs other than slowness in initiation of movement. The most intense akinesia and rigidity has followed large lesions. Where rigidity in flexion has followed after a long interval, I suspect that the lesion has enlarged because of delayed vascular changes, even after as long as seven years (Alexander 1942), and even forty-nine years in the report of Yakovlev (1944).

Focal Subthalamic Lesions

Discussion of the involuntary movements of *hemiballismus* resulting from lesions in the subthalamic nucleus will have to be omitted, except to emphasise that the characteristic movement involves a rotary element at proximal joints. This rotary element also appears in the posthemiplegic chorea associated with some types of thalamic lesion, and in the “ midbrain ” tremor so well described by Holmes (1904). When progressive lesions affect the general region of the midbrain tegmentum, rigid extension and internal rotation of all limbs eventually appears. This is the most common type of “ decerebrate rigidity ” encountered in man. Cathala (1922) has described a unilateral example resulting from tumour of the tectal region.

General Conclusions

In this necessarily abbreviated account of the general aspects of the symptomatology of diseases of the basal ganglia I have emphasised the diffuse nature of the pathology of such diseases, and their general tendency to produce involuntary movements that gradually make transition to abnormal postures. These two features are of special importance, for one of the most baffling aspects of these syndromes has been the inability of the physiologist to reproduce them by surgical or electrolytic lesions. It has not been appreciated that focal necrotic lesions of the putamen and globus pallidus can in man produce the terminal states that are seldom reached by degenerative diseases of the same structures. In particular I would stress the akinetic mute state of general flexion of all limbs, with pronated wrists and extended fingers, that is characteristic of severe destruction of the globus pallidus (“ pallidal syndrome ”). In milder degrees there is associated tremor of parkinsonian type. In contrast the more rigid flexion of upper limbs and extension of the lower limbs, greatly intensified by suspending the patient free of contact with body surface, is characteristic of destruction of the putamen and caudate nucleus (“ striatal syndrome ”). Lesser degrees of this disorder are characterised by athetosis and “ mobile spasm ”. With these two basic postural changes in mind their physiological meaning, and the significance of the disorders of movement that are associated with them, may be approached.

(*The references will appear at the end of the second lecture.*)

“ The more efficient society becomes at rapidly modifying our environment and our ways of life, the more unpredictable are the responses of man to the new conditions of his own making. In order to meet its professional responsibilities, medicine must add to its preoccupation with disease the study of the responses of normal man to the rapidly changing environment. It must supplement the knowledge of pathology with a new science which might be called biological technology. At least, this is the conviction which has led me, a bacteriologist, to focus my thoughts increasingly on the factors, external and internal, which condition the response of man to the microbes which are an ubiquitous part of his environment.”
—René J. Dubos. *J. Amer. med. Ass.* 1960, 174, 505.

HYPERSENSITIVITY TO MILK AND SUDDEN DEATH IN INFANCY

W E PARISH * A M BARRETT
B A Cantab , B V Sc Lpool M D Cantab
OF THE DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAMBRIDGE

R R A COOMBS
Ph D Cantab , M R C V S Edin
DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAMBRIDGE

MAVIS GUNTHER
M D Cantab
RESEARCH WORKER, OBSTETRIC DEPARTMENT,
UNIVERSITY COLLEGE HOSPITAL, LONDON, W C 1

FRANCIS E CAMPS
M D Lond , D T M & H
READER IN FORENSIC MEDICINE, DEPARTMENT OF FORENSIC MEDICINE,
LONDON HOSPITAL MEDICAL COLLEGE, E 1

IN a review of the possible causes of sudden death in infancy, Barrett (1954) suggested that of such cases "perhaps the majority are due to the inhalation of regurgitated food into the lungs" The inhaled food might not cause death by directly obstructing the air-passages an amount of milk too small to cause immediate asphyxia might excite an inflammatory reaction accompanied by pulmonary œdema, or the absorption of undue amounts of milk derivatives into the blood-stream might cause a state of shock

Such effects of inhaled food or vomit, if they occur, might be due either to an inherent toxicity of the inhaled material when it enters the body by this abnormal route, or to an anaphylactic type of reaction resulting from antigenic sensitisation

We present some experimental evidence which suggests that the second, but not the first, of these two mechanisms is indeed a possible cause of sudden death in infancy The hypothesis is that some infants may be in a hypersensitive state from the development of antibodies to the proteins of milk absorbed from the alimentary tract Infants often regurgitate stomach contents while asleep, and should some of this material be aspirated into the respiratory tract of an infant which has become hypersensitive, the result might be fatal

There is no doubt that most infants fed on cow's milk develop antibodies to the proteins of the milk Gunther, Aschaffenburg, Matthews, Parish, and Coombs (1960) using a sensitive technique—the coated tanned red-cell test of Boyden (1951)—showed milk antibodies in normal children aged 7–97 weeks in a titre up to 1000 with a modal distribution around a titre of 64

There thus seems to be ample evidence that the majority of infants are immunised to some degree or other to the proteins of cow's milk, and the possibility exists that these or other types of antibody may sensitise the tissues of the infants Anderson and Schloss (1923) showed that in infants with some types of nutritional disorders, milk proteins were absorbed via the alimentary tract and that subsequently precipitins to milk protein could be shown in the infants' sera, and these antibodies could sensitise guineapigs passively to anaphylaxis According to Clein (1958), up to 6% of infants during the first few months of their lives are allergic to cow's milk

Parish, Barrett, and Coombs (1960) showed that administration of milk over the glottis into the larynx of unsensitised conscious guineapigs was for all intents and purposes without clinical effect On the other hand, a small amount of milk dropped into the larynx of sensitised guineapigs resulted in a characteristic anaphylactic reaction often leading to death The reaction itself and the pathological findings in such animals were those of frank anaphylaxis and did not resemble those seen in human cot-death cases If, however, the guineapigs were lightly anæsthetised—an experimental condition used to simulate the condition of the sleeping child—milk introduced into the larynx had quite a different effect In the unsensitised guineapigs there was no untoward effect, and even in the sensitised animals there was a complete absence of the usual features of anaphylaxis seen in a conscious animal Very soon after introducing the milk preparations into the larynx of an anæsthetised sensitised guineapig, the animal stopped breathing without any signs of struggle Death sometimes occurred immediately, but the majority of animals took deep breaths at 10–30-second intervals for a variable period Death was preceded by a short period of more rapid breathing, each respiratory effort being shallower than the preceding one, until, with a final nose-twitching, the animal died Others lingered for 20–60 minutes before death took place, or normal respiration was gradually resumed This sequence of events became recognised as characteristic, and was reproducible on challenge of all the anæsthetised sensitised animals The pathological findings in the animals which died resembled those in human cot-death cases

In the present paper we have tried to relate our experimental results more directly to the condition in man (1) Sera from actual cases of cot death have been examined for their level of milk antibodies, as shown by the coated tanned red-cell test, in order to see if the distribution of levels is higher, as would be expected, than in randomly selected infants of comparable age (2) To test our hypothesis that the aspirated milk proteins originate as a regurgitation from the stomach, experiments have been performed on anæsthetised sensitised guineapigs in which the stomach contents recovered from cases of cot death were introduced into the respiratory tract Only stomach contents from infants known to have been bottle-fed at the time of death were used (3) Experiments have been performed to see if the individual milk proteins can produce a lethal effect (4) The pathological findings in guineapigs killed in this way are compared with those in cases of human cot death

Materials and Methods

These have been described in detail in two previous papers (Parish et al 1960, Gunther et al 1960)

Milk and Milk Proteins

As National dried milk powder is the product given to the majority of bottle-fed infants, it was employed as the source of milk proteins in our previous studies In the present work this product was again used as the sensitising antigen and the soluble proteins of the reconstituted powder used to coat the tannic-acid-treated *red cells in the serological tests for milk* antibodies

The isolated proteins of cow's milk—namely, casein, α-lactalbumin, and β-lactoglobulin—were prepared as described by Gunther et al (1960) and were kindly supplied by Dr R Aschaffenburg

Testing Sera for Antibodies

The method was basically the coated tanned red-cell technique of Boyden modified as described by Gunther et al (1960) The tanned red-cells were coated by exposing them to a 0 5% solution of protein antigen

Sensitisation of Guineapigs and Challenge

The guineapigs each received one intraperitoneal injection

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* Elmore Medical Research Fellow, University of Cambridge

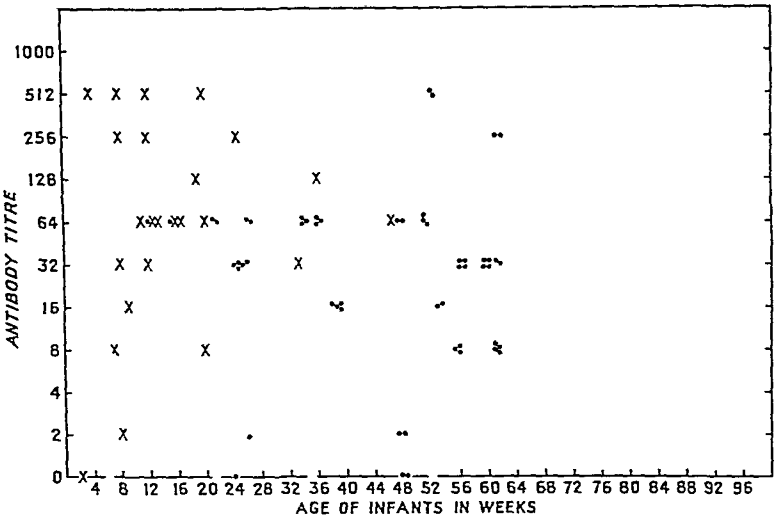

Fig 1—Titres of serum-antibody to cow's milk proteins at various ages in 24 ' cot-death ' cases (X) and in 286 normal infants (●)

A strict comparison of the two categories is not possible for the reasons stated in the test

of 1 ml reconstituted milk powder 2% w/v The inoculum consisted of the soluble and insoluble material

In experiments with human stomach-contents the animals were challenged on the 18th day after injection In experiments with milk proteins they were challenged on the 69th day

Anæsthesia

Pentobarbitone (' Nembutal ') was used as the anæsthetic in a dose of 0 01 ml per 20 g body-weight given intraperitoneally The depth of anæsthesia was such that the corneal reflex was very weak or just absent and the pedal reflex still present This was usually achieved in 15 minutes after injecting the pentobarbitone

Challenge via the respiratory tract—This was designed to mimic, as closely as possible, the accidental inhalation of regurgitated stomach contents by the sleeping infant The method has been fully described and illustrated by Parish et al (1960) With the aid of a gag and an illuminated nasal speculum, the mouth was opened and the entrance to the pharynx exposed While the tongue was depressed by a thin metal spatula, the milk or other challenging antigen was introduced over the glottis from a specially shaped blunt needle attached to a syringe When the animal inspired through the mouth it was possible to see the epiglottis which was the guide to the site of injection With practice it was possible to deposit the milk drop by drop over the glottis so that it was inhaled even when the larynx was invisible to the operator This procedure caused the minimum amount of damage to the respiratory tract

Experimental Study

Serum Antibody Levels

Using coated tanned red cells Gunther et al (1960) tested the sera of 286 normal children aged 7–97 weeks (fig 1) Nearly all the sera contained measurable antibody to cow's milk proteins In distribution the mode fell around a titre of 64 Approximately 4% had a titre of 256, 1% a titre of 512, and one serum had a titre of 1000 The plot of serum titre against the age in weeks of the child is shown in fig 1

We have now tested sera from 24 cases of cot death for the titre of antibodies to cow's milk Only those cases of sudden death were included which, on the pathologist's report, could be considered as " cot-death " cases These infants were known to have been bottle-fed at the time of death, and milk was found in their stomachs at post mortem

The serum titres of antibody to cow's milk in the cot-death cases are also shown in fig 1 where the distribution can be seen in relation to that found in normal infants

The number of cases available so far is not sufficient for a final assessment, nor is the mode of selection in the two categories appropriate for a strict comparison between the serum levels in normal infants and in the cot-death cases In the first place approximately 32% of the normal infants were known to be mainly breast-fed at 6 weeks of age, while the cot-death cases studied were all bottle-fed at the time of death Moreover, the blood from normal infants was collected under ideal conditions and the sera frozen to −15°C within 5 hours of bleeding, while the blood from cot-death cases was obtained post mortem and often had considerable precipitates which had to be centrifuged out before testing However the high titres found in the sera of the majority of cot-death cases are in keeping with the possibility that, had these infants aspirated milk into their respiratory tracts, a lethal hypersensitivity reaction, as seen experimentally in guineapigs, might have occurred

We are not suggesting that the level of serum antibody is necessarily a measure of the degree of sensitivity, although for the type of anaphylactic reaction envisaged this cannot be excluded It does indicate, however, that the infants have received a considerable antigenic stimulation with cow's milk and are, for this reason, potentially sensitised to these proteins

Effect of Stomach Contents on Sensitised Guineapigs

In our previous experiments (Parish et al 1960) National dried milk was used as the material for challenge In the present paper we report a similar experiment but the material used was stomach contents from actual cot-death cases in which the infant's last feed had been from the bottle This was used because, in the hypothesis we put forward, we believe regurgitated stomach contents are the source of the aspirated material initiating the lethal reaction

In this experiment both sensitised and unsensitised (control) guineapigs were lightly anæsthetised with an intraperitoneal injection of pentobarbitone Approximately 15 minutes later, when the desired state of anæsthesia had been reached, 0 25 ml of a 1/2 dilution of stomach contents (0 125 ml of the original contents) was introduced into the larynx Stomach contents from 4 cases of cot death were used The tenaciousness of this material necessitated its dilution with an equal volume of saline to avoid mechanical obstruction of the respiratory tract of the guineapig, which is, of course, much narrower than that of the human infant The stomach contents were obtained from dead infants aged 2, 4, 8, and 22 weeks The larger lumps found in the stomach of the oldest child were first broken down in a Griffith grinder

TABLE I—CLINICAL EFFECTS OF INHALING STOMACH CONTENTS FROM HUMAN COT-DEATH CASES BY NORMAL AND BY PREVIOUSLY SENSITISED GUINEA-PIGS LIGHTLY ANÆSTHETISED TO SIMULATE SLEEP

Challenge with stomach contents of dead infant	Dose of diluted stomach contents	Sensitised guineapigs		Unsensitised guineapigs	
		Reactions	Deaths	Reactions	Deaths
A aged 2 weeks	0 25 ml	D D D D + + −	4/5	+ − − − −	0/5
B, aged 4 weeks	0 25 ml	D D D + + −	3/5	− − − − −	0/5
C, aged 8 weeks	0 25 ml	D D D D	4/4	− − − −	0/4
D aged 22 weeks	0 25 ml	D D D D − −	4/5	+ + − ∸ −	0/5

Scale of severity of clinical effects
D=death
+ + + =severe respiratory embarrassment just insufficient to be fatal
+ − =definite clinical disturbance but not severe
− =one or two signs of respiratory embarrassment but always mild
— =no response

HYPERSENSITIVITY TO MILK AND SUDDEN DEATH IN INFANCY

W E Parish * A M Barrett
B A Cantab , B V Sc Lpool M D Cantab
OF THE DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAMBRIDGE

R R A Coombs
Ph D Cantab , M R C V S Edin
DEPARTMENT OF PATHOLOGY, UNIVERSITY OF CAMBRIDGE

Mavis Gunther
M D Cantab
RESEARCH WORKER, OBSTETRIC DEPARTMENT,
UNIVERSITY COLLEGE HOSPITAL, LONDON, W C 1

Francis E Camps
M D Lond , D T M & H
READER IN FORENSIC MEDICINE, DEPARTMENT OF FORENSIC MEDICINE,
LONDON HOSPITAL MEDICAL COLLEGE, E 1

In a review of the possible causes of sudden death in infancy, Barrett (1954) suggested that of such cases " perhaps the majority are due to the inhalation of regurgitated food into the lungs " The inhaled food might not cause death by directly obstructing the air-passages an amount of milk too small to cause immediate asphyxia might excite an inflammatory reaction accompanied by pulmonary œdema, or the absorption of undue amounts of milk derivatives into the blood-stream might cause a state of shock

Such effects of inhaled food or vomit, if they occur, might be due either to an inherent toxicity of the inhaled material when it enters the body by this abnormal route, or to an anaphylactic type of reaction resulting from antigenic sensitisation

We present some experimental evidence which suggests that the second, but not the first, of these two mechanisms is indeed a possible cause of sudden death in infancy The hypothesis is that some infants may be in a hypersensitive state from the development of antibodies to the proteins of milk absorbed from the alimentary tract Infants often regurgitate stomach contents while asleep, and should some of this material be aspirated into the respiratory tract of an infant which has become hypersensitive, the result might be fatal

There is no doubt that most infants fed on cow's milk develop antibodies to the proteins of the milk Gunther, Aschaffenburg, Matthews, Parish, and Coombs (1960) using a sensitive technique—the coated tanned red-cell test of Boyden (1951)—showed milk antibodies in normal children aged 7–97 weeks in a titre up to 1000 with a modal distribution around a titre of 64

There thus seems to be ample evidence that the majority of infants are immunised to some degree or other to the proteins of cow's milk, and the possibility exists that these or other types of antibody may sensitise the tissues of the infants Anderson and Schloss (1923) showed that in infants with some types of nutritional disorders, milk proteins were absorbed via the alimentary tract and that subsequently precipitins to milk protein could be shown in the infants' sera, and these antibodies could sensitise guineapigs passively to anaphylaxis According to Clein (1958), up to 6% of infants during the first few months of their lives are allergic to cow's milk

Parish, Barrett, and Coombs (1960) showed that administration of milk over the glottis into the larynx of unsensitised conscious guineapigs was for all intents and purposes without clinical effect On the other hand, a small amount of milk dropped into the larynx of sensitised guineapigs resulted in a characteristic anaphylactic reaction often leading to death The reaction itself and the pathological findings in such animals were those of frank anaphylaxis and did not resemble those seen in human cot-death cases If, however, the guineapigs were lightly anæsthetised—an experimental condition used to simulate the condition of the sleeping child—milk introduced into the larynx had quite a different effect In the unsensitised guineapigs there was no untoward effect, and even in the sensitised animals there was a complete absence of the usual features of anaphylaxis seen in a conscious animal Very soon after introducing the milk preparations into the larynx of an anæsthetised sensitised guineapig, the animal stopped breathing without any signs of struggle Death sometimes occurred immediately, but the majority of animals took deep breaths at 10–30-second intervals for a variable period Death was preceded by a short period of more rapid breathing, each respiratory effort being shallower than the preceding one, until, with a final nose-twitching, the animal died Others lingered for 20–60 minutes before death took place, or normal respiration was gradually resumed This sequence of events became recognised as characteristic, and was reproducible on challenge of all the anæsthetised sensitised animals *The pathological findings in the animals which died resembled those in human cot-death cases*

In the present paper we have tried to relate our experimental results more directly to the condition in man (1) Sera from actual cases of cot death have been examined for their level of milk antibodies, as shown by the coated tanned red-cell test, in order to see if the distribution of levels is higher, as would be expected, than in randomly selected infants of comparable age (2) To test our hypothesis that the aspirated milk proteins originate as a regurgitation from the stomach, experiments have been performed on anæsthetised sensitised guineapigs in which the stomach contents recovered from cases of cot death were introduced into the respiratory tract Only stomach contents from infants known to have been bottle-fed at the time of death were used (3) Experiments have been performed to see if the individual milk proteins can produce a lethal effect (4) The pathological findings in guineapigs killed in this way are compared with those in cases of human cot death

Materials and Methods

These have been described in detail in two previous papers (Parish et al *1960*, Gunther et al *1960*)

Milk and Milk Proteins

As National dried milk powder is the product given to the majority of bottle-fed infants, it was employed as the source of milk proteins in our previous studies In the present work this product was again used as the sensitising antigen and the soluble proteins of the reconstituted powder used to coat the tannic-acid-treated red cells in the serological tests for milk antibodies

The isolated proteins of cow's milk—namely, casein, α-lactalbumin, and β-lactoglobulin—were prepared as described by Gunther et al (1960) and were kindly supplied by Dr R Aschaffenburg

Testing Sera for Antibodies

The method was basically the coated tanned red-cell technique of Boyden modified as described by Gunther et al (1960) The tanned red-cells were coated by exposing them to a 0 5% solution of protein antigen

Sensitisation of Guineapigs and Challenge

The guineapigs each received one intraperitoneal injection

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* Elmore Medical Research Fellow, University of Cambridge

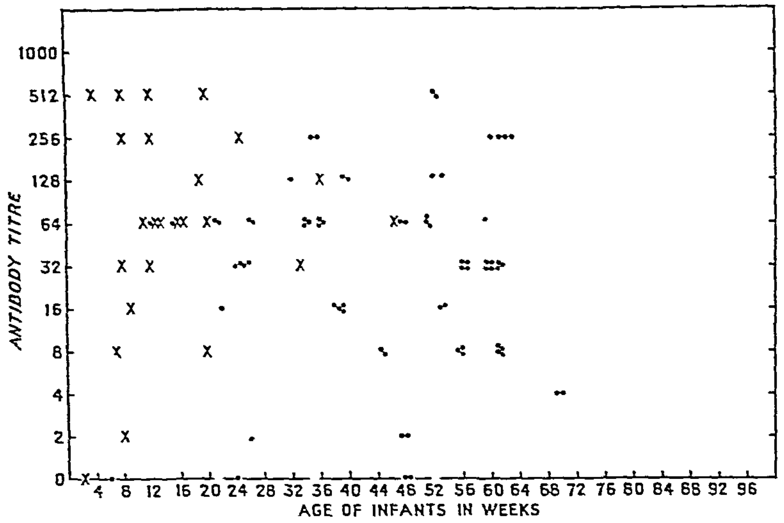

Fig 1—Titres of serum-antibody to cow's milk proteins at various ages in 24 'cot-death' cases (X) and in 286 normal infants (●)

A strict comparison of the two categories is not possible for the reasons stated in the test

of 1 ml reconstituted milk powder 2% w/v The inoculum consisted of the soluble and insoluble material

In experiments with human stomach-contents the animals were challenged on the 18th day after injection In experiments with milk proteins they were challenged on the 69th day

Anæsthesia

Pentobarbitone ('Nembutal') was used as the anæsthetic in a dose of 0 01 ml per 20 g body-weight given intraperitoneally The depth of anæsthesia was such that the corneal reflex was very weak or just absent and the pedal reflex still present This was usually achieved in 15 minutes after injecting the pentobarbitone

Challenge via the respiratory tract—This was designed to mimic, as closely as possible, the accidental inhalation of regurgitated stomach contents by the sleeping infant The method has been fully described and illustrated by Parish et al (1960) With the aid of a gag and an illuminated nasal speculum, the mouth was opened and the entrance to the pharynx exposed. While the tongue was depressed by a thin metal spatula, the milk or other challenging antigen was introduced over the glottis from a specially shaped blunt needle attached to a syringe When the animal inspired through the mouth it was possible to see the epiglottis which was the guide to the site of injection With practice it was possible to deposit the milk drop by drop over the glottis so that it was inhaled even when the larynx was invisible to the operator This procedure caused the minimum amount of damage to the respiratory tract.

Experimental Study

Serum Antibody Levels

Using coated tanned red cells Gunther et al (1960) tested the sera of 286 normal children aged 7–97 weeks (fig 1) Nearly all the sera contained measurable antibody to cow's milk proteins In distribution the mode fell around a titre of 64 Approximately 4% had a titre of 256, 1% a titre of 512, and one serum had a titre of 1000 The plot of serum titre against the age in weeks of the child is shown in fig 1

We have now tested sera from 24 cases of cot death for the titre of antibodies to cow's milk Only those cases of sudden death were included which on the pathologist's report, could be considered as "cot-death" cases These infants were known to have been bottle-fed at the time of death, and milk was found in their stomachs at post mortem

The serum titres of antibody to cow's milk in the cot-death cases are also shown in fig 1 where the distribution can be seen in relation to that found in normal infants

The number of cases available so far is not sufficient for a final assessment, nor is the mode of selection in the two categories appropriate for a strict comparison between the serum levels in normal infants and in the cot-death cases In the first place approximately 32% of the normal infants were known to be mainly breast-fed at 6 weeks of age, while the cot-death cases studied were all bottle-fed at the time of death Moreover, the blood from normal infants was collected under ideal conditions and the sera frozen to −15°C within 5 hours of bleeding, while the blood from cot-death cases was obtained post mortem and often had considerable precipitates which had to be centrifuged out before testing However the high titres found in the sera of the majority of cot-death cases are in keeping with the possibility that, had these infants aspirated milk into their respiratory tracts, a lethal hypersensitivity reaction, as seen experimentally in guinea-pigs, might have occurred

We are not suggesting that the level of serum antibody is necessarily a measure of the degree of sensitivity, although for the type of anaphylactic reaction envisaged this cannot be excluded It does indicate, however, that the infants have received a considerable antigenic stimulation with cow's milk and are, for this reason potentially sensitised to these proteins

Effect of Stomach Contents on Sensitised Guineapigs

In our previous experiments (Parish et al 1960) National dried milk was used as the material for challenge In the present paper we report a similar experiment but the material used was stomach contents from actual cot-death cases in which the infant's last feed had been from the bottle This was used because, in the hypothesis we put forward, we believe regurgitated stomach contents are the source of the aspirated material initiating the lethal reaction

In this experiment both sensitised and unsensitised (control) guineapigs were lightly anæsthetised with an intraperitoneal injection of pentobarbitone Approximately 15 minutes later, when the desired state of anæsthesia had been reached, 0 25 ml of a 1/2 dilution of stomach contents (0 125 ml of the original contents) was introduced into the larynx Stomach contents from 4 cases of cot death were used The tenaciousness of this material necessitated its dilution with an equal volume of saline to avoid mechanical obstruction of the respiratory tract of the guineapig, which is, of course, much narrower than that of the human infant The stomach contents were obtained from dead infants aged 2, 4, 8, and 22 weeks The larger lumps found in the stomach of the oldest child were first broken down in a Griffith grinder

TABLE I—CLINICAL EFFECTS OF INHALING STOMACH CONTENTS FROM HUMAN COT-DEATH CASES BY NORMAL AND BY PREVIOUSLY SENSITISED GUINEA-PIGS LIGHTLY ANÆSTHETISED TO SIMULATE SLEEP

Challenge with stomach contents of dead infant	Dose of diluted stomach contents	Sensitised guineapigs		Unsensitised guineapigs	
		Reactions	Deaths	Reactions	Deaths
A, aged 2 weeks	0 25 ml	D D D D ———	4/5	— — — — —	0/5
B, aged 4 weeks	0 25 ml.	D D D —— —	3/5	— — — — —	0/5
C, aged 8 weeks	0 25 ml.	D D D D	4/4	— — — —	0 4
D aged 22 weeks	0 25 ml.	D D D D ——	4/5	— — — — —	0 5

Scale of severity of clinical effects
D=death.
———=severe respiratory embarrassment just insufficient to be fatal
——=definite clinical disturbance but not severe.
—=one or two signs of respiratory embarrassment but always mild.
—=no response

In the unsensitised guineapigs no deaths, and in the great majority of cases no effects, were observed On the other hand most of the sensitised animals exhibited the syndrome already described and died silently, without any struggle, and in a very short time Three animals recovered after a protracted period during which there were long spells of apnœa interrupted only by occasional weak gasps One of the sensitised animals was apparently unaffected The results are summarised in table I

Effect of Milk Proteins on Sensitised Guineapigs

In our earlier report (Parish et al 1960) we recorded the level of milk antibodies and the clinical sensitivity to challenge with milk at 17, 38, 64, and 92 days after a single sensitising injection Although in some animals the level of serum-antibody appeared to fall with the passage of time the animals were as sensitive clinically to the aspiration of milk on the 92nd day as they were earlier We wished to see if a similar lethal reaction could be produced by the individual component proteins of cow's milk

The guineapigs were sensitised as before by injecting intraperitoneally 2% w/v reconstituted National dried milk in a dose of 1 ml On the 69th day they were challenged via the respiratory tract while under light anæsthesia with 0 25 ml of (*a*) the soluble proteins in 10% w/v reconstituted milk powder (approximately 1% soluble proteins), (*b*) 1% casein, (*c*) 1% α-lactalbumin, or (*d*) 1% β-lactoglobulin The day before challenge each animal was bled and the serum subsequently tested for antibodies to reconstituted dried milk, and to the component protein with which the guineapig was challenged

The results of the serological tests, and the clinical effects on challenge are recorded in table II Casein, as might be expected, proved to be as effective as whole milk in producing lethal reactions In one of the previous papers (Gunther et al 1960) similarly sensitised guineapigs tested 17 days after injection had antibodies to α-lactalbumin but none to β-lactoglobulin In the present experiment no antibodies could be shown to α-lactalbumin 69 days after injection Clinically only very mild reactions were produced on challenging with α-lactalbumin, but with β-lactoglobulin the reactions were as severe as with casein or whole milk

TABLE II—LEVEL OF SERUM ANTIBODY TO MILK PROTEINS ON 69TH DAY AFTER INJECTION AND CHALLENGE OF SENSITISED GUINEAPIGS WITH COMPONENT PROTEINS OF COW'S MILK

Guinea pig	Challenged with	Serum antibody titre to				Clinical effect on challenge‡
		Reconst National dried milk	Casein	α lact albumin	β lacto-globulin	
1	Soluble material in reconstituted National dried milk*	16				+ +
2		16				D
3		32				+ + +
4		16				D
5						D
6	Casein†	8	16			D
7		16	16			+ +
8		128	64			D
9		16	16			D
10		16	16			D
11	α lactalbumin†	8		0		+
12		32		0		+
13		32		0		+
14		8		0		W
15		16		0		—
16	β lactoglobulin†	16			0	D
17		8			0	+ +
18		4			0	D
19		64			32	D
20		64			4	D

0 indicates a titre < 2

‡ Scale of severity of clinical effects—see table I

* Made up 10% w/v—approximately 1% soluble protein

† A 1% solution

Of thirty unsensitised (control) anæsthetised guineapigs challenged with soluble or insoluble milk preparations (Parish et al 1960) no reaction was observed in twenty six—one showed a very mild reaction and two a moderate reaction One animal died but on subsequent investigation its serum was shown to contain what appeared to be a naturally occurring antibody to cow's milk proteins to a titre of 16

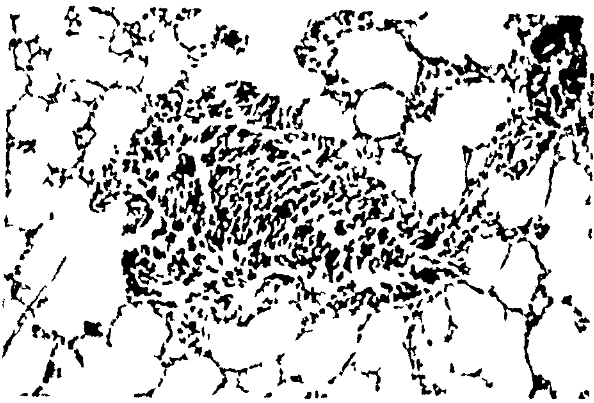

Fig 2—A bronchiole of anæsthetised sensitised guineapig which died soon after the introduction into its trachea of 0 25 ml of diluted (50%) stomach contents from a case of cot death (Hæmatoxylin and eosin ×120)

The bronchiole is so full of desquamated epithelial cells that in the photograph it is scarcely recognisable

We have thus shown that lethal reactions can be produced with casein and β-lactoglobulin On the other hand only mild reactions were obtained with α-lactalbumin However, further guineapigs will have to be tested at different periods after sensitisation before this protein can be considered less noxious than the other two

Pathological Findings in Sensitised Guineapigs

The histopathology of the lungs of sensitised guineapigs which died after inhalation, when anæsthetised, of total reconstituted dried milk, or its soluble or insoluble fractions, has already been described (Parish et al 1960) All the changes observed in the lungs of similarly sensitised guineapigs which died after the inhalation of casein or β-lactoglobulin closely resembled those in the earlier experiments In those sensitised animals challenged with β-lactoglobulin or casein, the chief features were generalised congestion with occasional areas of partial collapse, and serous exudate or œdematous transudate Cellular infiltration in the œdematous areas, or in the peribronchial, or periarteriolar connective tissue consisted chiefly of mononuclear cells Many of these were macrophages with variable numbers of lymphocytes and, in some animals, plasma-cells, but there were few polymorphonuclear cells A common finding was the desquamation of large numbers of single, intact, apparently normal, epithelial cells of the bronchial wall into the lumen of the small bronchioles

The histopathological changes in the lungs of sensitised anæsthetised guineapigs which had died as a result of inhaling small amounts of the stomach contents obtained from cot-death cases were similar to those observed in sensitised animals inhaling milk Generalised congestion was usual, but there was only an occasional small area of œdema and little cellular infiltration The infiltrating cells were chiefly macrophages, though there was an increased number of polymorphonuclear leucocytes—more than observed in animals challenged by milk The majority of the leucocytes were eosinophils, and in some preparations they were found also in the peribronchial connective tissue There was some evidence that the bronchioles and arterioles had undergone contraction, but further study of this feature is required Many of the medium-sized and smaller bronchioles contained large numbers of desquamated cells, sometimes these completely filled the lumen (fig 2) Bronchioles thus affected could be found in all the lung material, but the number varied from animal to animal The trachea was usually congested and in some cases infiltrated by eosinophils, the epithelium of the trachea was not desquamated

The unsensitised—i e , normal anæsthetised control guineapigs which had inhaled the stomach contents obtained from the same human subjects, and subsequently killed by an overdose of pentobarbitone—had different histopathological changes in their lungs There were large areas of partial collapse and œdema, or serous exudate, infiltrated with moderate numbers of macrophages and polymorphs of both the heterophil and eosinophil type All areas of the lung were congested and there was an occasional small hæmorrhage into the alveoli The epithelium of the majority of the bronchioles was intact, if it was not, the desquamation was in the form of sheets or strips of epithelium, and for the most part the individual cells were not detached from one another (fig 3)

The differences in degree of œdema and cellular infiltration between the unsensitised and sensitised guineapigs challenged with human stomach contents probably depend on the time that the irritant material remained in the living animal The majority of the sensitised animals died within 5 minutes, and all within 10 minutes, whereas the unsensitised animals were killed about 3 hours after challenge Previous experiments on normal animals revealed that the mode of killing by pentobarbitone did not cause changes of this type

The histopathological findings in sensitised guineapigs, dying after inhalation of milk proteins, are very similar to those described and illustrated in cot death by Barrett (1954) and Stewart (1957) The lungs of cot-death subjects are usually congested, and the engorgement of the capillaries is often accompanied by œdema, small hæmorrhages, foci of partial collapse, and an increase in the number of macrophages in the alveoli The walls of the bronchi are infiltrated by lymphocytes and plasma cells, sometimes there are also smaller numbers of polymorphonuclear leucocytes Desquamation of the bronchial epithelium is commonly seen (figs 4 and 5) and is often of the type described by Bodian and Heslop (1956), who thought that the presence within the bronchi of large numbers of individual desquamated cells embedded in mucus was characteristic of cot death, although it did not occur in every case

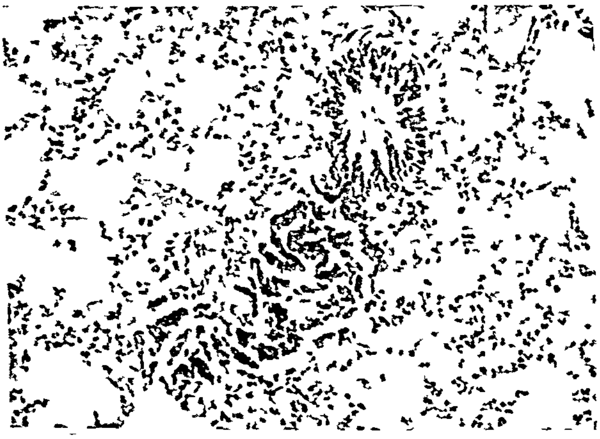

Fig 3—Bronchioles of an unsensitised guineapig which was killed 3 hours after receiving the same dose of the same stomach contents as fig 2. (H & E ×120)

The introduction of the stomach contents was without clinical effect The upper bronchiole is normal, the bronchiolar epithelium of guineapigs is normally more folded than that of man In the lower bronchiole, the lumen is occupied by strips of detached epithelium, but the appearance is different from that in fig 2

All of these histopathological features of cot death were also seen in the sensitised anæsthetised guineapigs which died after inhalation of small amounts of milk, or of stomach-contents containing milk Perhaps the most significant common finding was the presence of large numbers of individual intact epithelial cells in the lumina of the bronchioles The appearance was the same as that described by Bodian and Heslop (1956) except that in the guineapigs there was little if any mucus This difference may be due to an anatomical difference between man and guineapig, for there are very few mucous glands in the trachea and bronchi of the guineapig, and few goblet-cells in the epithelium Another difference between the human and the animal material is that in the guineapigs no desquamation of epithelium was observed in the trachea, though it occasionally occurred in the large bronchi Desquamation of epithelium is, however, a common postmortem change, which would be expected to be greater in the human than in the animal material because of the unavoidably longer interval between death and necropsy

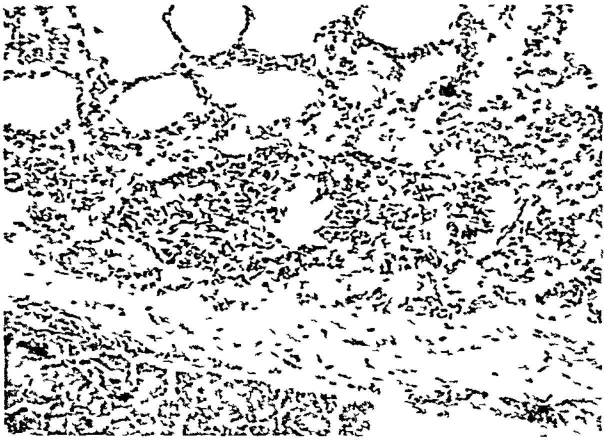

Fig 4—Bronchiole from case of cot death, showing lumen filled with desquamated epithelial cells (H & E. ×100)

Discussion

Sudden death of infants is by no means uncommon, and the Registrar General's data showed that in England and Wales in 1955, there were 1432 such deaths accounting for 20 5% of the 6993 deaths between the ages of 2 weeks and 2 years (Banks 1958)

The usual history is that of a baby dying in its sleep As a rule the babies are between 1 month and 6 months of age, though the incidence appears to be highest at about 3 months These deaths are attributed by many to a fulminating infection, although attempts to demonstrate a causal organism, either bacteria or virus, have been unsuccessful in most cases (Banks 1958)

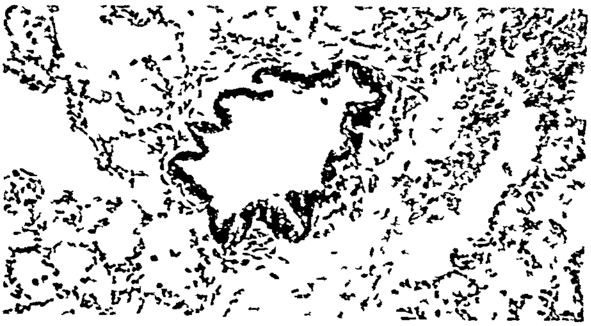

Fig 5—Bronchiole of infant believed to have died of suffocation (H & E. ×100)

The epithelium is intact except at the top left, where it has become partially detached Such detachment often occurs post mortem

The most common foreign proteins to which a baby is exposed are those of cow's milk, either as fresh milk, or as a preserved-milk product, which is also a constituent of proprietary preparations for infants It has previously been shown that babies may be sensitised to milk products (Anderson and Schloss 1923, Tallerman 1934) and this sensitivity may cause disease on contact with the milk antigen (Clein 1958) In the preliminary experiments, where examination was made of the sera of normal babies between 7 and 97 weeks of age for agglutinating antibodies to cow's milk, the large majority were found to have been " immunised " to some degree or other, and their tissues were probably sensitised by some form of antibody as a result of this immunisation (Gunther et al 1960) When, as in fig 1, the antibody titres to milk in the serum of babies believed to be typical cases of cot death are superimposed on those obtained from normal infants, it can be seen that in any age group the titres of the cot-death cases tend to be high when compared with the normal, indicating that a considerable degree of sensitivity could be present

In experiments performed on guineapigs (Parish et al 1960), which have been confirmed by the data presented in this paper, it was found that sensitised guineapigs in an anæsthetised state died after inhalation of milk proteins Death was not typical anaphylactic shock as observed in the conscious state, but the animal, without any struggle, stopped breathing either at once or after a brief episode of irregular respiration Animals not sensitised to milk could inhale up to 1 0 ml without significant effect The histopathological changes following challenge of the sensitised animals had much in common with those described in cases of cot death in infants

It has thus been demonstrated that sensitised animals, when unconscious, can be killed quickly, silently, and without trace of struggle by the inhalation of whole milk, or, at least, by two constituent proteins of milk, casein and β-lactoglobulin

It is well known that babies frequently regurgitate small quantities of food during sleep and often leave traces on the pillow In our hypothesis it is suggested that inhalation of regurgitated material can induce a lethal reaction, and that only small amounts need be aspirated The quantity aspirated by the infant may be of the order of 1 0 ml, on a comparison of the weights of the test guineapigs and cot-death subjects

We have been able to show that many babies have some antibody to cow's milk, and that guineapigs with a similar serum-antibody level can be killed quietly by aspiration of small quantities of milk

If the challenge agent in babies were food material from the stomach regurgitated during sleep, it had to be shown that this material retained its antigenic properties sufficiently to cause shock on contact with tissues sensitised to milk This was found to be so The stomach contents taken from 4 cases of cot death in which the infants were known to be bottle-fed, when inhaled in small amounts by lightly anæsthetised guineapigs sensitised to milk proteins, resulted in death, quietly and without struggle, in 15 of the 19 challenged animals The histopathological features were similar to those observed in cot death of infants An equal number of anæsthetised guineapigs, not sensitised to milk proteins, which had inhaled the same stomach-content material displayed no effects, or scarcely appreciable respiratory embarrassment, and there were no deaths

These experiments provide a model of a possible cause of cot death in infants If the serum level of antibody is a valid indication, the majority of babies are sensitised to some degree to cow's milk, and it is possible that a normal healthy baby may be put to bed, and, during its sleep regurgitate and inhale sufficient material to cause an antigen-antibody reaction in the sensitised tissue of the lungs, causing physiological and pathological changes resulting in the death of the infant

Further investigation of this problem is being undertaken An attempt is being made to prove that an antigen-antibody reaction has taken place in the lungs of such infants and that this reaction is of sufficient magnitude to cause death The nature or the degree of the sensitivity may be an important factor, for the number of babies that have a substantial titre of circulating antibodies to milk is large compared to the small number of cot-death cases, though another limiting factor may be the frequency with which aspiration occurs Nevertheless, the fact that babies do become sensitised to cow's milk proteins, and that inhalation of this material could conceivably be the cause of cot death in a young infant, should be another inducement to breast-feed young babies where practicable

Summary

Experimental evidence is presented to support the hypothesis that cot death in infants may be due to an anaphylactic type of reaction consequent on the inhalation of cow's milk proteins regurgitated from the stomach during sleep

Serological tests show that most infants fed on cow's milk develop antibodies to milk proteins

Experiments on anæsthetised guineapigs, sensitised to the proteins of cow's milk, show that many such animals die rapidly and without struggling when a small quantity (0 25 ml) of (*a*) cow's milk, (*b*) stomach contents from cases of " cot death ", (*c*) a 1% solution of casein, or (*d*) a 1% solution of β-lactoglobulin is introduced into the air passages

The histopathological changes in the lungs of the experimental animals resemble those found in cases of cot death

We wish to acknowledge the helpful discussion with the members of the steering committee and the scientific subcommittee of the " Enquiry into sudden death in infancy " under the respective chairmanships of Prof Leslie Banks and Sir Samuel Bedson and to thank this body and the Nuffield Foundation for a grant to cover the cost of animals used in these experiments They are most grateful to Dr H R M Johnson for his help in the collection of material from cot-death cases, and to Dr N R Butler and the pædiatric staff, University College Hospital, for their help in obtaining serum-samples

We thank Miss Brenda Disbrey and her staff for the painstaking work in the preparation of the histological material, Mr B W Gurner for drawing fig 1, and Mr S W Patman for taking the photographs

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EFFECT OF PHENINDIONE AND BED REST ON BLOOD COAGULABILITY FOLLOWING A HIGH-FAT INTAKE

G. A. McDonald
M.D. Aberd.
LECTURER IN MEDICINE

H. W. Fullerton
M.A., M.D. Aberd., F.R.C.P., F.R.C.P.E.
REGIUS PROFESSOR OF MEDICINE

UNIVERSITY OF ABERDEEN

Recently we have shown that, when careful attention is paid to technique, the recalcified-plasma-clotting (R.P.C.) time is an accurate measure of in-vitro coagulability (McDonald and Fullerton 1958a). With further experience of this technique, in more than 200 samples of plasma, duplicate readings have given a mean difference of less than 3 seconds and a maximum difference of 7 seconds. A smooth non-traumatic venepuncture is essential. When this is achieved the mean difference between samples obtained from both arms in 15 patients was only 3.5 seconds, and in only 1 case was this difference greater than 8 seconds, which we take as the upper limit of experimental error (McDonald and Fullerton 1958a). Difficulty in venepuncture shortens the R.P.C. time. This is clearly shown in table I, which gives simultaneous R.P.C. times for both arms in 14 patients. The venepuncture was satisfactory in one arm; in the other it was unsatisfactory in that tissue trauma was produced, either inadvertently or by design. It is seen that the readings in the samples obtained by unsatisfactory venepuncture were consistently much shorter, the mean difference being 28.3 seconds.

TABLE I—SIMULTANEOUS R.P.C. TIMES (SEC.) IN BOTH ARMS: VENEPUNCTURE UNSATISFACTORY IN ONE ARM

Subject no.	Satisfactory arm	Unsatisfactory arm	Difference
1	103	75	28
2	124	110	14
3	130	115	15
4	87	73	14
5	127	93	34
6	147	96	51
7	117	91	26
8	137	110	27
9	124	59	65
10	123	103	20
11	95	47	48
12	130	113	17
13	131	116	15
14	115	93	22
Means	120.7	92.4	28.3

By this technique we have shown that (1) a high-fat breakfast containing 85 g. animal-fat (bacon, eggs, butter, tea with milk and sugar) resulted in a pronounced shortening of the R.P.C. times measured 3 and 4 hours after the meal (McDonald and Fullerton 1958a), (2) a similar reduction occurred after approximately the same amount of vegetable fat (McDonald and Fullerton 1958a), and (3) the effect of the high animal-fat breakfast was almost completely abolished by a moderate amount of physical activity (McDonald and Fullerton 1958b).

TABLE II—GROUP 1: RECENT CARDIAC INFARCTION, PHENINDIONE, BED REST

Subject no.	Fasting	3½ hr.	Difference
1	126.5	117.5	+9
2	163	162	+1
3	151	143	+8
4	146.5	133.5	+13
5	134	131	+3
6	133	136.5	−3.5
7	142	131	+11
8	177	176	+1
9	138	146	−8
10	160	159	+1
Means	147.1	143.5	+3.6

The object of the experiments reported here was primarily to assess the effect of therapeutic doses of phenindione on this increase in coagulability following a high fat intake.

TABLE III—GROUP 2: NON-CARDIAC DISORDERS, NO PHENINDIONE, BED REST

Subject no.	Fasting	3½ hr.	Difference
1	104.5	74.5	+30
2	122	74	+48
3	102.5	69.5	+33
4	125.5	59.5	+66
5	111	76	+35
6	111.5	90	+21.5
7	102	72.5	+29.5
8	114	102	+12
9	116	100.5	+15.5
10	107	86	+21
Means	111.6	80.4	+31.2

Clinical Material and Methods

The methods used in these experiments and the details of the animal-fat breakfast (fat content, approximately 85 g.) have been described previously (McDonald and Fullerton 1958a). Four groups have been studied in this way:

Group 1.—10 inpatients at rest in bed, with recent cardiac infarction, treated with phenindione for periods varying from 4 to 18 days.

Group 2.—10 inpatients at rest in bed, with non-cardiac disorders, and not treated with phenindione.

Group 3.—10 outpatients with previous cardiac infarction who had had long-continued therapeutic doses of phenindione for periods varying between 12 and 45 months.

Group 4.—10 outpatients who had had a cardiac infarction and had received 1 mg. phenindione daily for periods ranging between 20 and 41 months. This group was drawn from the controls in the Medical Research Council (1959) trial of long-term anticoagulant administration after cardiac infarction.

The subjects in groups 3 and 4 were allowed to undertake some physical activity, in contrast to the subjects in groups 1 and 2 who were confined to bed both during and for several days before the experiment. They reached hospital by walking varying distances and by using public transport, and, after the high-fat breakfast had been taken, they were allowed to walk short distances from time to time in the ward corridors.

TABLE IV—GROUP 3: OLD CARDIAC INFARCTION, PHENINDIONE, AMBULANT

Subject no.	Fasting	3½ hr.	Difference
1	148	146	+2
2	123	125.5	−2.5
3	144	119.5	−5.5
4	187	174	+13
5	140	134	+6
6	188.5	176	+12.5
7	144.5	139	+5.5
8	127	134	−7
9	141	141.5	−0.5
10	130	131	−1
Means	147.3	145	+2.3

In groups 1 and 3 the one-stage "prothrombin-time" was maintained at 2 to 2½ times the control level, whereas in group 4 it was within the normal range. No patient in group 2 had a disorder likely to be associated with an abnormality of blood coagulation.

In addition to estimations of the R.P.C. times, the degree of lipæmia in each sample of plasma was measured by assessing the turbidity by a modification of the method described by Schwartz et al. (1952). Direct measurement of light transmittance was obtained with a Spekker photoelectric absorptio-

TABLE V—GROUP 4 OLD CARDIAC INFARCTION, 1 MG PHENINDIONE, AMBULANT

Subject no	Fasting	$3^1/_2$ hr	Difference
1	116	116	0
2	102	92	+10
3	152	130	+22
4	124	97	+27
5	138	117	+21
6	145	125	+20
7	139	118	+21
8	130	110 5	+19 5
9	116 5	96	+20 5
10	105	98 5	+6 5
Means	126 7	110	+16 7

TABLE VI—MEAN PERCENTAGE INCREASE IN TURBIDITY AND REDUCTION OF R P C TIME (SEC) IN THE FOUR GROUPS

Group no	Increase in turbidity	Reduction in R P C time
1	205	3 6
2	337	31 2
3	80	2 3
4	123	16 7

meter and expressed as the direct scale reading Glass cuvettes with a 2 mm light path and a blue filter (Ilford Spectrum Blue, 602) with maximum transmittance at 4700 Å were used

Results

The results are presented in tables II–V, which show the R P C times of all the subjects fasting and during the phase of lipæmia $3^1/_2$ hours after the meal It is seen that in subjects in groups 1 and 3 who were receiving therapeutic doses of phenindione, the fasting R P C times were slightly prolonged but the high-fat meal had no consistent effect on the R P C times during the lipæmic phase $3^1/_2$ hours after the meal In group 1 the greatest reduction was only 13 seconds and the mean reduction 3 6 seconds In group 3 the corresponding figures are 13 seconds and 2 3 seconds In group 4, receiving only 1 mg phenindione daily, the results were strikingly different In 8 of the 10 subjects the R P C times $3^1/_2$ hours after the high-fat meal were considerably shorter than the readings during fasting, and the mean reduction was 16 7 seconds This result is similar to that found in a group of 16 students who undertook little physical activity after the high-fat breakfast (mean reduction 23 8 seconds) (McDonald and Fullerton 1958b) In group 2 the mean reduction in R P C time $3^1/_2$ hours after the meal was still greater—31 2 seconds This is similar to the results found previously in 11 subjects confined to bed, in them the mean reduction in R P C time 3 hours after the high-fat breakfast was 39 seconds, and at 4 hours 35 seconds (McDonald and Fullerton 1958a)

Discussion

The results demonstrate that the ingestion of a high-fat breakfast by patients receiving therapeutic doses of phenindione (groups 1 and 3) does not produce the acceleration of the R P C time found in subjects not receiving this drug (groups 2 and 4) So far as we know this action of phenindione has not been demonstrated previously, its mechanism is obscure Clearly, however, it does not depend entirely upon an alteration in the degree of plasma turbidity during the lipæmic phase Table VI shows the mean percentage increase in turbidity $3^1/_2$ hours after the high-fat meal, and the mean decrease in the R P C time in the four groups of subjects In both groups of ambulant patients (groups 3 and 4) the increase in turbidity was less than in the patients at rest in bed (groups 1 and 2) But in group 1 the increase in turbidity was greater than in group 4, whereas the mean reduction in R P C time in group 1 was negligible and in group 4 it was considerable

A comparison of the findings in groups 2 and 4 has confirmed our previous impression that the reduction in R P C time is considerably greater in subjects confined to bed in hospital It seems that even the small amount of physical activity undertaken before and after the ingestion of the high-fat breakfast by the subjects observed as outpatients (group 4) offsets to some extent the increase in coagulability during the phase of lipæmia Further studies along these lines are at present in progress

The practical importance of the effect of phenindione which we have demonstrated is at present conjectural Because of the differences between the process of clotting in vitro and intravascular thrombosis, it is perhaps unwise to draw firm conclusions from results obtained with the R P C test and other laboratory tests of blood coagulability Nevertheless one essential feature common to clotting in vitro and intravascular thrombosis is fibrin formation, and it is not unreasonable to suggest that factors which can be shown to accelerate this process in vitro may also operate when intravascular thrombosis occurs

Many physicians treat patients with cardiac infarction with phenindione and by restricting their fat intake If shortening of the R P C time following a high-fat meal reflects increased coagulability in vivo and, therefore, an increased tendency to thrombus formation, there may be nothing to be gained by lowering the fat intake of patients receiving phenindione Moreover, it seems possible that the beneficial effect of phenindione in cardiac infarction may be due partly to its action in abolishing the increase in coagulability after high-fat meals

Summary

Shortening of the recalcified-plasma-clotting (R P C) time following the ingestion of a high-fat meal was *not* found in patients receiving therapeutic doses of phenindione

In subjects not receiving phenindione the shortening was greater in patients confined to bed than in those who were ambulant

We are grateful to Sister I M Cowie, ward 1, Aberdeen Royal Infirmary, for much help, and to the patients for their cooperation

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MEDICAL TREATMENT OF MYCETOMA

W PETER COCKSHOTT
M D Edin , D M R D
SENIOR LECTURER IN RADIOLOGY, UNIVERSITY COLLEGE, IBADAN

A M RANKIN
M B Adelaide, M R C P , M R A C P , D T M & H
SENIOR REGISTRAR IN MEDICINE,
UNIVERSITY COLLEGE HOSPITAL, IBADAN

MYCETOMA is the name applied by H V Carter to a fungal infection prevalent in Southern India, which was locally termed Madura foot Although still often used for this low-grade fungal parasitism, the latter term is undesirable because it suggests an exclusive geographical and anatomical localisation

Mycetoma occurs predominantly in underdeveloped areas which have rudimentary medical facilities and often no auxiliary medical departments Thus we can hardly expect full mycological identification of the responsible organism in each case Ideally specific chemotherapy depends upon identification and culture of the organism, determination of its sensitivity to a range of drugs, and exhibition of the appropriate drug But even with the best of facilities culture is difficult and identification is a matter of experience and special training, whilst details of suitable drugs are at present mainly to be found in specialised journals, reports of their efficacy sometimes being difficult to evaluate Consequently an outlook of therapeutic nihilism has prevailed as far as mycetoma is concerned, and the treatment has almost invariably been surgical ablation of the affected tissues

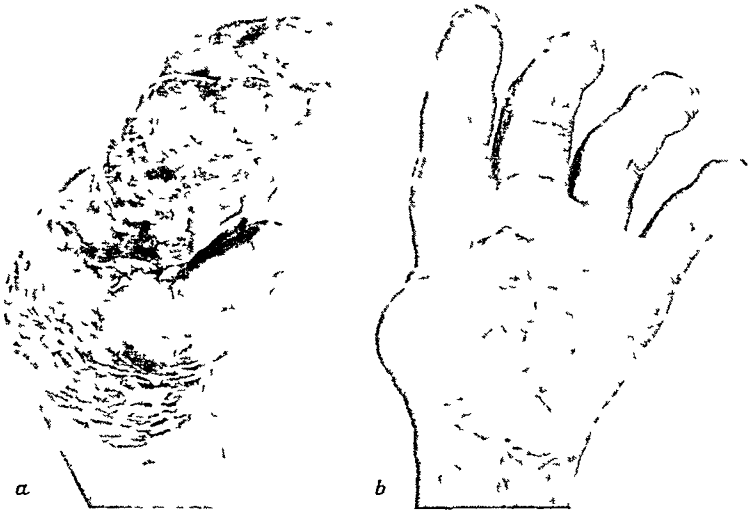

Fig 1—Left hand (*a*) on admission, and (*b*) 6 months later

Although not a killing disease, mycetoma causes a fair amount of morbidity and disablement—disablement which is little alleviated by amputation unless prostheses are available The effect upon a wage-earner and his family—the disease is primarily of active males—can well be disastrous

In these particular social and medical circumstances any drug advocated must have a wide range of effectiveness against the many possible causative organisms, and it must also be safe, cheap, and easy to administer A simple scheme of treatment, giving a satisfactory overall “ cure ” rate, is more likely to gain widespread acceptance than a more definitive but complex scheme, although a few cases may not respond to this shot-gun method Whatever the method there are still some fungi for which no specific therapy is yet known For those patients who fail to respond to chemotherapy amputation is still available

In Ibadan we have treated cases of mycetoma with a preliminary course of a wide-spectrum antibiotic, to eradicate the almost invariable secondary infection, combined with a long course of dapsone (diaminodiphenylsulphone), and, when feasible, with immobilisation of the affected part These patients were only admitted to hospital for a week or so until secondary infection had cleared, and they then continued to take dapsone, in a dosage of 100 mg b d , as outpatients After initial observation for a month they need only attend hospital every 3 months, and this regime may be continued for anything up to 2 years

Although surgery still plays a role in the treatment of mycetoma, it should not be invoked, except in special circumstances, until a reasonable course of medical treatment has been tried Orthopædic surgeons expect that bone and joint tubercle and leprosy require long-continued exhibition of drugs, and the same attitude should eventually prevail in the treatment of mycetoma Early surgery is probably justifiable in strictly localised forms of the disease, particularly the nodular superficial varieties caused by the black-grain *Madurella mycetomi*

Eight of a group of eighteen cases which we treated in Ibadan without radical surgery have responded, showing closure of sinuses, and clinical and radiographic improvement, and they have returned to their previous work We have been unable to follow all the patients because some defaulted or continued their course elsewhere—these have been assumed to be failures To know whether the “ clinical cure ” persists will require a longer follow-up, but at least these patients still have the use of their limbs

The dramatic response which can follow this treatment is shown by the following case-histories

Case 1—A 40-year-old Yoruba farmer came to hospital complaining of progressive swelling of the left hand, and of multiple discharging sinuses, which had been present for 3 years These had prevented him from working for the past year He was ashamed of his enormous foul-smelling hand, and kept it covered up and hidden within his gown

Multiple sinuses and ulcerated areas were present over both surfaces of the hand, and much foul discharge was exuding No grains could be seen The axillary lymph-glands on the same side were large and tender A radiograph of the hand disclosed extensive periosteal new bone enveloping the metacarpals and phalanges, and this was considered typical of a nocardial type of mycetoma, with secondary infection No fungal elements were observed in the pus, and only *Escherichia coli* was isolated on culture Biopsy of skin and subcutaneous tissues revealed a chronic inflammatory reaction, but no grains could be demonstrated Despite these negative bacteriological findings a definite clinical diagnosis of mycetoma was made

Tetracycline, 250 mg q i d was given for a week, and in addition dapsone 100 mg b d was started The patient continued on the drug for 2 years A month after starting treatment the hand had returned to more normal proportions and all the sinuses had healed Within 6 months of his first attendance the patient was again at work in the fields His hand is now completely healed, but the range of movement is limited partly by scarring but more so by degree of subluxation of his wrist which causes passive insufficiency of his flexors Now that the lesion is quiescent orthopædic procedures are envisaged to give a more useful hand (fig 1)

Case 2—A Yoruba tailor, aged 45, attended hospital because of progressive swelling of his left hand for 7 months and ulceration of his left axilla for the previous 3 months Because of this disability he had been unable to work The left hand was greatly swollen with multiple puckered sinuses exuding a thin serous discharge There were areas of ulceration in the axilla and on the chest wall (fig 2) A radiograph of the hand showed typical changes of nocardial-type diffuse mycetoma A biopsy specimen was taken but the tissue only revealed a chronic inflammatory reaction, and no grains A nocardia species was obtained from culture of the pus, but full identification was not possible as the strain died out *Esch coli* also grew from the pus

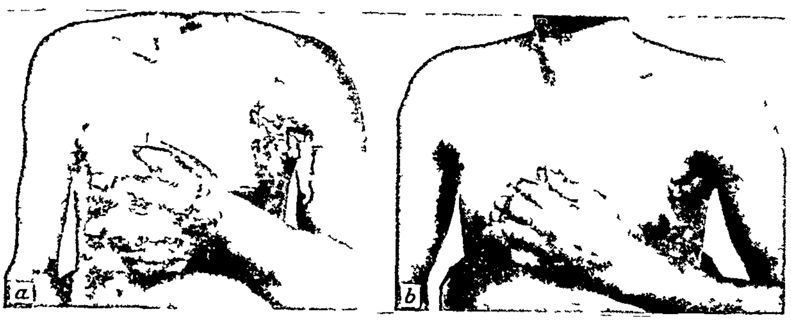

Fig 2—Appearance of case 2 (*a*) on admission, and (*b*) 7 months later

This clinical type of mycetoma, with early invasion of the thorax, is very serious and occasionally fatal, and justifies energetic treatment Penicillin 2 million units was given daily for 3 months, and at the same time dapsone 100 mg was given twice a day by mouth The ulceration in the axilla slowly healed during the first 3 months, and the sinuses of the hand had closed at the end of 6 months The patient now has an efficient hand and is again working as a tailor The course of dapsone lasted 2 years, during which time he showed no evidence of toxic reactions

Case 3 —A 20-year-old farmer came to the surgical outpatient department with a swollen discharging left foot Sinuses were present on the greatly swollen dorsum of the foot, and the inguinal glands on that side were enlarged and hard A radiograph revealed a destructive lesion of the second metatarsal, and some periosteal reaction near the head of this bone, which was reported as being probably due to mycetoma As no fungal elements could be recovered from the discharge, the lesion was considered tuberculous by the clinician and accordingly treated with *p*-aminosalicylic acid and isoniazid for 3 months without improvement

The patient was then admitted to hospital, and the foot was explored, with removal of the metatarsal and curetting of the sinuses The bone showed on section grains morphologically identical with *Nocardia braziliensis* The patient was given dapsone 100 mg b d for a period of 18 months 4 months after the operation the foot had completely healed and the patient had returned to work Surgery was probably not necessary in this case, but this form of local resection, with chemotherapeutic cover, may have led to more rapid healing

Discussion

Mycetoma is caused by a wide variety of organisms of different genera and species, and it presents by its very nature several features which tend to render it resistant to chemotherapy

Firstly, although the pathological processes may vary in degree of severity from the localised *M mycetomi* infections to the infiltrating lesions of *Allescheria boydii* and *Streptomyces pelletieri*, yet, in virtually all cases, the fungal elements occur within relatively avascular tissue resulting from scarring and local endarteritic changes

Secondly, once sinuses have developed pyogenic secondary organisms invade the lesion

Thirdly, the disease is caused by a variety of species each differing from the rest in its drug sensitivity, and even isolates of the same species may vary in their response from case to case

Because of the wide variety of causative organisms a single drug is unlikely to prove effective against all the possible organisms of mycetoma A further factor to be borne in mind is the geographical distribution of the different organisms A complete survey of this is impossible here, but, for example, in Southern Arabia and the Sudan the common organisms are *M mycetomi*, *Strep somaliensis* and *Strep pelletieri*, whereas in Western Nigeria *N brasiliensis*, *M mycetomi* and *All boydii* are probably the most frequent

The best therapeutic regime will probably vary according to the main species in any particular locality We do not suggest that our scheme of treatment is the only one, or even the best, but we have found it effective in salvaging limbs, and it is cheap Though blind therapy in a sense, it is suited to the conditions of practice where mycetoma is most frequent The basic principle of a course of antibiotics and prolonged drug administration, combined with immobilisation by sling or plaster-of-paris, seems to us rational Much that was written on the chemotherapy of this disease before 1950 is now merely of historical interest Some of the more recent developments have been reviewed by one of us (Cockshott 1957) and this paper can be consulted for more detailed references

Dapsone, though first synthesised in 1907, found no pharmacological application until 1937, when it was discovered to be effective in treating experimental streptococcal infections but it was too toxic for man in the dosage then being employed Dapsone possesses a degree of antituberculous activity, but its main use has been in the treatment of leprosy caused by acid-fast mycobacteria Ochoa found that dapsone was effective in vitro against the acid-fast nocardia, which causes some varieties of mycetoma, and systemic nocardiosis Encouraged by these tests he started treating mycetoma due to *N brasiliensis* with this drug, and the results were excellent (Ochoa 1955, Ochoa and Macatola 1955) Various other workers (Halde and Newstrand 1955, Mackinnon et al 1958) have shown that dapsone is effective in causing inhibition of growth of *M grisea*, *Strep maduræ*, and *Strep somaliensis*, as well as *N brasiliensis* The antifungal activity of this drug probably depends upon substrate competition for paraminobenzoic acid (Cockshott 1957)

Although the dosage of dapsone we have used may seem high, it appears to be safe We advise close observation during the first month to enable early detection of exfoliative dermatitis or hæmolytic anæmia in the occasional case One of our patients developed exfoliative dermatitis, and his therapy had to be discontinued

Summary

A plea is made for a more optimistic outlook in the treatment of mycetoma A regime based on a short course of wide-spectrum antibiotic and prolonged treatment with dapsone by mouth has been found effective In nearly half our cases, this treatment has avoided the need for amputation and enabled the patient to get back to work

We extend our thanks to the physicians and surgeons of University College Hospital, Ibadan, who have referred cases to us, and to Mr Frank Speed, of the medical illustration department, for the photographs

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EVALUATION OF THROMBOTEST IN THE CONTROL OF ANTICOAGULANT THERAPY

H. LEMPERT
M.D., M.Sc. Manc., A.R.I.C.
CONSULTANT PATHOLOGIST IN CHARGE OF
THE ANTICOAGULANT THERAPY SERVICE

L. POLLER
M.D. Manc.
SENIOR REGISTRAR IN PATHOLOGY

From the Department of Clinical Pathology,
Manchester Royal Infirmary

CONTROL of anticoagulant therapy with coumarin or indanedione drugs has been based for many years on the one-stage prothrombin-time test of Quick (1935). Oral anticoagulant drugs undoubtedly lower the production of prothrombin, but the term "prothrombin-time" is somewhat of a misnomer, since it is factor VII which is mainly measured. Fortunately Quick's test is very sensitive to changes in factor VII activity. Drug dosage is so adjusted that prothrombin-times of $1\frac{1}{2}$–$2\frac{1}{2}$ times normal are obtained within a few days and maintained in this so-called therapeutic range. Quick (1938) demonstrated the hyperbolic relationship between prothrombin-times and prothrombin activity, normal prothrombin activity being 100%. Thus the "therapeutic range" is about 15–30% of normal if a saline extract of acetone-dried rabbit or human brain is used as thromboplastin reagent in the test.

During oral anticoagulant treatment hæmorrhages or further thromboses have sometimes been reported even where the greatest care has been taken to keep within the therapeutic range. In recent years it has been shown that, during treatment, factors involved in "intrinsic" blood-thromboplastin production—e.g., Christmas factor (factor IX), Prower-Stuart factor (factor X), and possibly others—are reduced. Quick's test does not register changes in Christmas factor because of the powerful tissue thromboplastin used.

Some workers are of the opinion that heparin-clotting-time methods give a better indication of impending complications (Soulier and le Bolloch 1951, Poller 1954) but, for technical reasons, such tests are not suited to the daily routine control of large numbers of patients on anticoagulants.

Owren (1959), in his 'Thrombotest' method, has modified the one-stage technique in order to produce a method capable of measuring "intrinsic" blood-thromboplastin factors as well as prothrombin and factor VII. The thrombotest reagent contains a thromboplastin of relatively weak activity, and it is claimed to possess some sensitivity to changes in Christmas-factor levels.

We made our present investigations to assess the value of the thrombotest method for the control of patients on phenindione ('Dindevan') therapy as compared with Quick's test and the prothrombin and proconvertin (P & P) test of Owren and Aas (1951). In view of the claims that thrombotest was sensitive to changes in blood-thromboplastin factors, it seemed essential to include a thromboplastin-generation test (T.G.T.).

Methods of Study

Forty-three inpatients undergoing phenindione anticoagulant therapy were studied. They were divided into two groups, A and B.

In group A, comprising thirty-one patients, dosage of the anticoagulant was based on the Quick prothrombin-time method, and observations were made of the effect on the P & P method, the T.G.T., and thrombotest. The clinical conditions included in this group were:

Coronary thrombosis	13
Pulmonary embolism	2
Venous thrombosis	2
Cerebral vascular disorders	3
Angina pectoris	8
Peripheral artery occlusion	3

In group B, which consisted of twelve patients, dosage was based on the result of thrombotest, and the observation was confined to the effect on the Quick prothrombin-time method and T.G.T. The cases included in this group were:

Coronary thrombosis	10
Pulmonary embolism	1
Prophylactic therapy	1

In group A, 415 blood specimens were tested during 530 days of treatment. In group B, 154 blood specimens were examined over 246 days' treatment.

Technique

Quick One-stage Prothrombin-time

Venous blood (5 ml.) was collected into a siliconed syringe (although siliconing of the syringe is not essential), and transferred to a bijou bottle containing a dried oxalate mixture (0·21 ml. of an aqueous solution containing 2·4% ammonium oxalate and 1·6% potassium oxalate dried at 37°C in an incubator for 36 hours). The blood and oxalates were thoroughly mixed. The blood was then centrifuged at 3500 r.p.m. in a 13×100 mm. test-tube for 5 minutes. The supernatant plasma was decanted into another tube. The thromboplastin reagent was prepared from acetone-dried human brain. A phenol-saline extract was prepared (Powell 1957) which gave normal prothrombin-times of 11–12 seconds. A dilution curve was obtained by the saline dilution of normal plasma, the results from six normal subjects were averaged. On this curve, readings of 19–30 seconds represented 30–15% prothrombin activity. The same batch of brain was used throughout the investigation. The calcium-chloride reagent used was 0·18% $CaCl_2$, and it was prepared from a stock 1% solution checked by chemical analysis. This reagent was warmed to 37°C before use.

The test proper consisted in pipetting 0·1 ml. thromboplastin reagent into a 10×70 mm. test-tube in a 37°C water bath, and allowing the reagent to warm up for at least five minutes. The reagent could be incubated up to 2 hours without deterioration. The test plasma (0·1 ml.) was then added, and the contents of the tube were mixed gently. Within 20 seconds of mixing, 0·1 ml. of the warm calcium chloride was added, a stopwatch being started simultaneously. The tube was tilted to and fro until a clot was seen to form. Three tests were made on each specimen, and the results averaged. All tests were performed within an hour of collecting the venous-blood specimen.

P & P Method of Owren and Aas (1951)

Venous blood (1·8 ml.) was collected into a siliconed syringe (although siliconing of the syringe is not essential), and transferred to a *siliconed* bijou bottle containing 0·2 ml. trisodium citrate (3·13%). The anticoagulant used in this test usually contains heparin to prevent activation of clotting factors by contact with glass. We preferred to use a siliconed container so that the same specimen of blood might also be used for the thrombotest, thus obviating the use of heparin which would interfere with the latter test.

The blood and citrate were thoroughly mixed, and the specimen was centrifuged in the same siliconed bijou bottle. Supernatant plasma (0·1 ml.) was removed immediately before the test, and the 1 in 10 dilution was prepared in the usual manner. The bovine plasma obtained from an abattoir was adsorbed twice with barium sulphate, as recommended by Biggs and Macfarlane (1957). The saline extract of human brain was obtained in the following way. Human brain was freed from meninges and blood-vessels, washed with distilled water, cut into small pieces, and transferred to a large mortar. Warm saline at 42°C was added in small quantities, and the tissue was pounded with a pestle In all 1500 ml of saline was added The thick supernatant suspension was distributed into 1 oz screw-capped universal containers, incubated at 37°C for 30 minutes, and then centrifuged to give a clear supernatant which was distributed into bijou bottles The bijou bottles were stored at −20°C This extract was found to give clotting times of 30–32 seconds with normal plasma A citrate-saline dilution curve was prepared in the usual way The same batch of thromboplastin reagent was used throughout the investigation

The same specimen of blood was used for both P & P test and thrombotest The thrombotest was always performed before the P & P test, removal of plasma for the P & P test could otherwise have interfered with the thrombotest by altering the red-cell volume

Thrombotest

Owren (1959) recommended that either venous or capillary blood could be used for this test We decided to use venous blood only, because with capillary blood there is always the danger of contamination of the specimen with a high concentration of tissue thromboplastin Non-wettable syringes and containers must be used for the collection of the venous-blood specimen, because contact with glass shortens the clotting times and gives misleading results for the assessment of anticoagulant dosage

Apparatus

Waterbath at 37°C, containing a metal test-tube rack with holes to accommodate 10×70 mm test-tubes

Pipette for measuring calcium chloride (11 ml) for reconstituting the lyophilised thrombotest reagent *

Pipette (0 5 ml) for thrombotest reagent *

Pipette (0 1 ml) for blood sample *

Syringes and bijou bottles siliconed with dimethyl dichlorosilane reagent in a fume cupboard The silicone reagent bottle was handled with protective rubber gloves The fumes are dangerous if inhaled The reagent was drawn into the syringes, left in contact for 1 minute, and returned to the stock bottle in the fume cupboard The bijou bottles were filled to the neck, and after 5 minutes the reagent was carefully decanted back into the stock bottle The barrels and plungers were separated and washed in slowly running tap water continuously for 10 days The bijou bottles were treated similarly A final rinse with distilled water was given, and the washings were found to be neutral with B D H universal indicator One coating with the silicone reagent seemed to provide a permanent non-wettable surface For convenience a 2 ml graduation mark was made on the exterior surface of the bijou bottles

Chemically clean 10×70 mm test-tubes

Reagents

Thrombotest reagent —The lyophilised reagent in an ampoule was reconstituted with the calcium-chloride solution (see below) by gently mixing and incubating the resulting suspension, at 37°C, in a water bath for 1 hour The reagent was gently mixed before use When not required the reagent ampoule was stoppered and stored at 4°C, it was found to be stable for 4 days if the precaution of storing at 4 C was carefully observed Four batches supplied by the manufacturers were used, and these gave different readings with normal venous blood Each batch was supplied with its own dilution curve Normal readings varied from 34 to 43 seconds with different batches of reagent

Calcium chloride (3 2 mM solution)

Venous blood was collected as for the P & P test with a siliconed syringe Thus the same specimen could be used for the two tests Venous blood (1 8 ml) was added to the 0 2 ml trisodium citrate (3 13%) anticoagulant in the graduated bijou bottle The contents were gently mixed In all other respects the technique was as described by Owren (1959)

Procedure

Thrombotest reagent (0 5 ml) was pipetted into a 10×70 mm test-tube and left to warm in the 37°C bath for at least 3 and not more than 30 minutes The venous-blood sample was gently mixed, and as 0 1 ml was pipetted into the tube containing the thrombotest reagent a stopwatch was started simultaneously The tube was gently tilted in the waterbath until a firm solid clot had formed The percentage activity was then read from the dilution curve supplied by the manufacturers of the reagent

Thromboplastin-generation Test

The procedure was as described by Biggs and Douglas (1953), except for the use of brain extract instead of platelet suspension (Bell and Alton 1954) The 6-minute reading was used for assessing the rate of thromboplastin generation The results were related to a dilution curve prepared each day from a normal subject The results of the T G T were plotted graphically for each patient during the course of treatment, and compared with the graphed results of the Quick, P & P, and thrombotest methods

The correlations between T G T and each of the three methods mentioned above were then broadly assessed as being good, moderate, or poor in the forty-three patients investigated

To check the constancy of the results of the T G T a control group, comprising six hospital patients with no clinical evidence of thrombosis, was studied daily for 10 days The test was found to give consistent results with the same batch of platelet substitute

Results

Detailed results are shown in table I

Group A

The patients in this group were controlled by the Quick test and were kept within the accepted therapeutic range (15–30% prothrombin activity) for over 80% of the period of treatment

All patients were tested before treatment and then daily until the therapeutic range was reached All results were included in the analysis, but had the initial results been excluded the proportion of tests within the therapeutic range would have been even higher

The P & P test and thrombotest correlated well throughout, but the results were not directly comparable with those of the Quick test Patients were within the P & P therapeutic range (10–30% activity) for only about half the period of treatment For the thrombotest, it has been suggested by Owren that the therapeutic range is also 10–30% activity Patients were only maintained within this thrombotest range for about two-thirds of the period of treatment

Many results were below the lower limit of the thrombotest and P & P therapeutic range—i e, less than 10% activity On the other hand, with the Quick test very few were below its lower limit—i e, *less than 15% prothrombin activity*

Group B

The patients in this group were controlled by thrombotest, and these results were compared with the results of the Quick test

TABLE I—COMPARISON OF THE RESULTS (IN TEST DAYS) OF QUICK, P & P, AND THROMBOTEST METHODS

Group	No of patients	Total no of test days	Total days treatment	Quick (range 15 to 30%)		P & P (range 10 to 30%)		Thrombotest (range 10 to 30 %)	
				Results above range	Results below range	Results above range	Results below range	Results above range	Results below range
A	31	415	530	76 (*18 3%*)	6 (*1 5%*)	16 (*3 9%*)	178 (*42 9%*)	12 (*2 9%*)	127 (*30 6 %*)
				within range *80 2* %		within range *53 2%*		within range *66 5*	
B	12	154	246	45 (*29 2%*)	1 (*0 7%*)			8 (*5 2%*)	29 (*18 8%*)
				within range *70 1%*				within range *76 0* %	

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* Pipettes specifically designed for the test can be obtained commercially if necessary

Over three-quarters of the patients were kept within the recommended 10–30% range The results with the Quick test were found to be different from those in group A. Thus the number above the upper therapeutic range—i e , over the 30% upper limit of the Quick test—was considerably higher

Results of Thromboplastin-generation Test

The correlation between the Quick test and T G T in group A was

Test	*Good*	*Moderate*	*Poor*
Quick	7	12	12
P & P	14	6	11
Thrombotest	13	8	10

and the correlation in group B was

Test	*Good*	*Moderate*	*Poor*
Quick	4	–	4
Thrombotest	6	2	4

Good correlation between the two tests was found in less than a quarter of the patients The P & P test and thrombotest, on the other hand, correlated well about twice as often. But the correlation was only moderate or poor in more than half the patients In figs 1 and 2 examples are given of good and poor correlation between the T G T and other tests

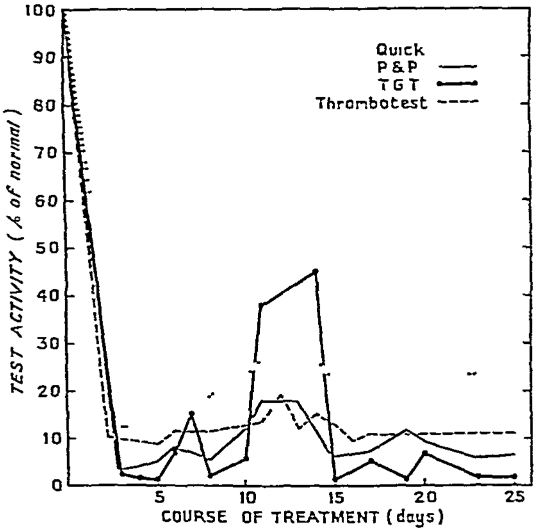

Fig 1—Good correlation between T G T and the three tests

Good correlation was usually found when there was much depression of the coagulation factors Thus, when the T G T , thrombotest, and P & P test correlated well, the Quick results were usually in the therapeutic range of 15–30% In contrast, where the Quick test showed results above 30% activity, correlation between the T G T and the other tests was relatively poor

In nineteen of the forty-three patients a fluctuating pattern of thromboplastin generation was observed during the course of phenindione treatment There was no obvious correlation between the T G T fluctuation and the Quick prothrombin activity or the dosage of anticoagulant

In a further six cases evidence of these fluctuations was doubtful The remaining sixteen cases showed no evidence of " spontaneous " fluctuation in the pattern of thromboplastin generation.

A fluctuating pattern of thromboplastin generation was considered to be present if a trend was observed in consecutive tests during treatment. The results were classed as doubtful where such a fluctuation was observed only in isolated tests Fig 3 shows a typical fluctuating thromboplastin-generation pattern, together with the results of the Quick, P & P, and thrombotest

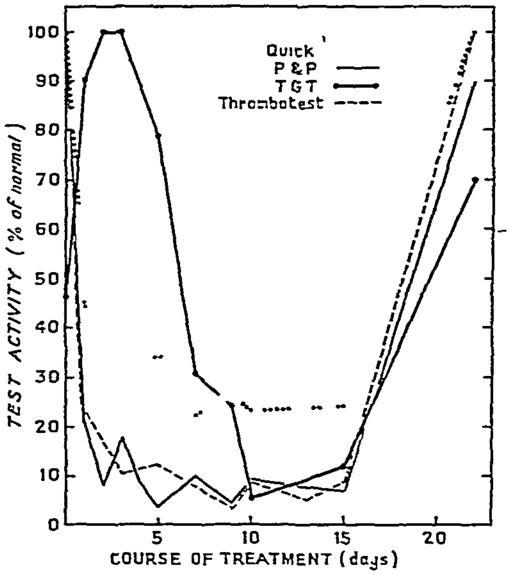

Fig 2—Poor correlation between T G T and the three tests

In contrast the six controls (hospital patients without clinical evidence of thrombosis) gave a consistent 100% thromboplastin generation in all estimations made over a 10-day period.

The forty-one treated patients were classified into 4 groups—i e., thrombotic (proved cases), doubtful thrombotic, non-thrombotic, and cases of angina pectoris The presence of fluctuating thromboplastin generation patterns in these groups is seen in table II, about 50% of the proved thrombotic cases showing these fluctuations

In eleven patients *before treatment*, the results of the T G T showed that thromboplastin generation was increased—i e , was above 100%—when compared with normal controls Six were patients with proved thrombosis, and four had suspected but not proved thrombosis One had angina pectoris In all these cases the Quick test, the P & P test, and thrombotest did not reflect this increase in thromboplastin activity In fact, in five cases thrombo-

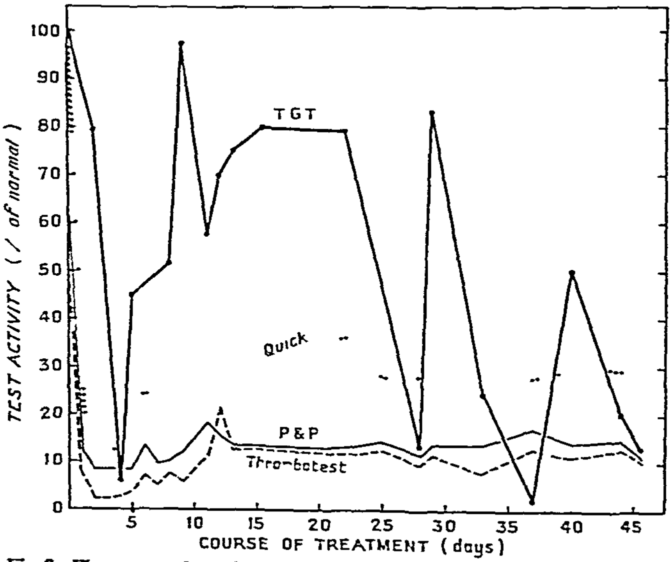

Fig 3—Fluctuating thromboplastin-generation pattern during phenindione treatment.

tissue was pounded with a pestle. In all 1500 ml. of saline was added. The thick supernatant suspension was distributed into 1 oz. screw-capped universal containers, incubated at 37°C for 30 minutes, and then centrifuged to give a clear supernatant which was distributed into bijou bottles. The bijou bottles were stored at −20°C. This extract was found to give clotting times of 30–32 seconds with normal plasma. A citrate-saline dilution curve was prepared in the usual way. The same batch of thromboplastin reagent was used throughout the investigation.

The same specimen of blood was used for both P. & P. test and thrombotest. The thrombotest was always performed before the P. & P. test, removal of plasma for the P. & P. test could otherwise have interfered with the thrombotest by altering the red-cell volume.

Thrombotest

Owren (1959) recommended that either venous or capillary blood could be used for this test. We decided to use venous blood only, because with capillary blood there is always the danger of contamination of the specimen with a high concentration of tissue thromboplastin. Non-wettable syringes and containers must be used for the collection of the venous-blood specimen, because contact with glass shortens the clotting times and gives misleading results for the assessment of anticoagulant dosage.

Apparatus

Waterbath at 37°C, containing a metal test-tube rack with holes to accommodate 10 × 70 mm. test-tubes.

Pipette for measuring calcium chloride (11 ml.) for reconstituting the lyophilised thrombotest reagent.*

Pipette (0.5 ml.) for thrombotest reagent.*

Pipette (0.1 ml.) for blood sample.*

Syringes and bijou bottles siliconed with dimethyl dichlorosilane reagent in a fume cupboard. The silicone reagent bottle was handled with protective rubber gloves. The fumes are dangerous if inhaled. The reagent was drawn into the syringes, left in contact for 1 minute, and returned to the stock bottle in the fume cupboard. The bijou bottles were filled to the neck, and after 5 minutes the reagent was carefully decanted back into the stock bottle. The barrels and plungers were separated and washed in slowly running tap water continuously for 10 days. The bijou bottles were treated similarly. A final rinse with distilled water was given, and the washings were found to be neutral with B.D.H. universal indicator. One coating with the silicone reagent seemed to provide a permanent non-wettable surface. For convenience a 2 ml. graduation mark was made on the exterior surface of the bijou bottles.

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Thrombotest reagent.—The lyophilised reagent in an ampoule was reconstituted with the calcium-chloride solution (see below) by gently mixing and incubating the resulting suspension, at 37°C, in a water bath for 1 hour. The reagent was gently mixed before use. When not required the reagent ampoule was stoppered and stored at 4°C, it was found to be stable for 4 days if the precaution of storing at 4°C was carefully observed. Four batches supplied by the manufacturers were used, and these gave different readings with normal venous blood. Each batch was supplied with its own dilution curve. Normal readings varied from 34 to 43 seconds with different batches of reagent.

Calcium chloride (3.2 mM solution).

Venous blood was collected as for the P. & P. test with a siliconed syringe. Thus the same specimen could be used for the two tests. Venous blood (1.8 ml.) was added to the 0.2 ml. trisodium citrate (3.13%) anticoagulant in the graduated bijou bottle. The contents were gently mixed. In all other respects the technique was as described by Owren (1959).

Procedure

Thrombotest reagent (0.5 ml.) was pipetted into a 10 × 70 mm. test-tube and left to warm in the 37°C bath for at least 3 and not more than 30 minutes. The venous-blood sample was gently mixed, and as 0.1 ml. was pipetted into the tube containing the thrombotest reagent a stopwatch was started simultaneously. The tube was gently tilted in the waterbath until a firm solid clot had formed. The percentage activity was then read from the dilution curve supplied by the manufacturers of the reagent.

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The procedure was as described by Biggs and Douglas (1953), except for the use of brain extract instead of platelet suspension (Bell and Alton 1954). The 6-minute reading was used for assessing the rate of thromboplastin generation. The results were related to a dilution curve prepared each day from a normal subject. The results of the T.G.T. were plotted graphically for each patient during the course of treatment, and compared with the graphed results of the Quick, P. & P., and thrombotest methods.

The correlations between T.G.T. and each of the three methods mentioned above were then broadly assessed as being good, moderate, or poor in the forty-three patients investigated.

To check the constancy of the results of the T.G.T. a control group, comprising six hospital patients with no clinical evidence of thrombosis, was studied daily for 10 days. The test was found to give consistent results with the same batch of platelet substitute.

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The patients in this group were controlled by thrombotest, and these results were compared with the results of the Quick test.

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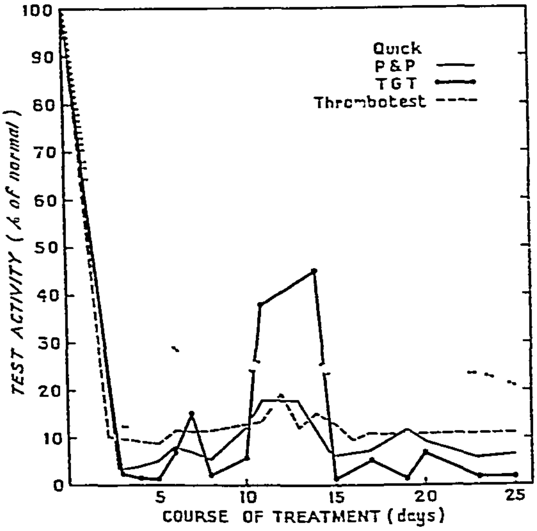

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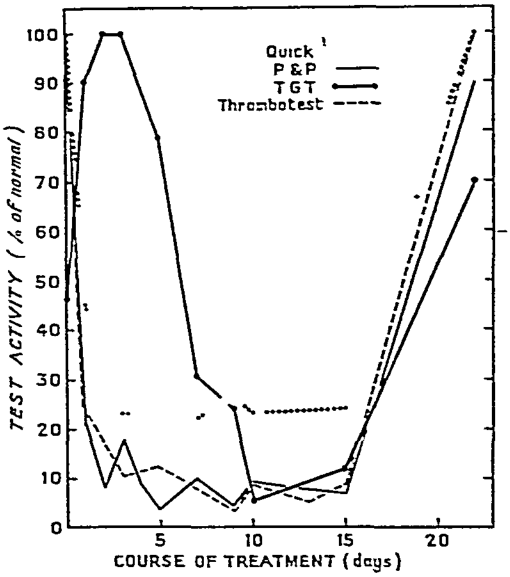

Fig 2—Poor correlation between T G T and the three tests.

In contrast the six controls (hospital patients without clinical evidence of thrombosis) gave a consistent 100% thromboplastin generation in all estimations made over a 10-day period

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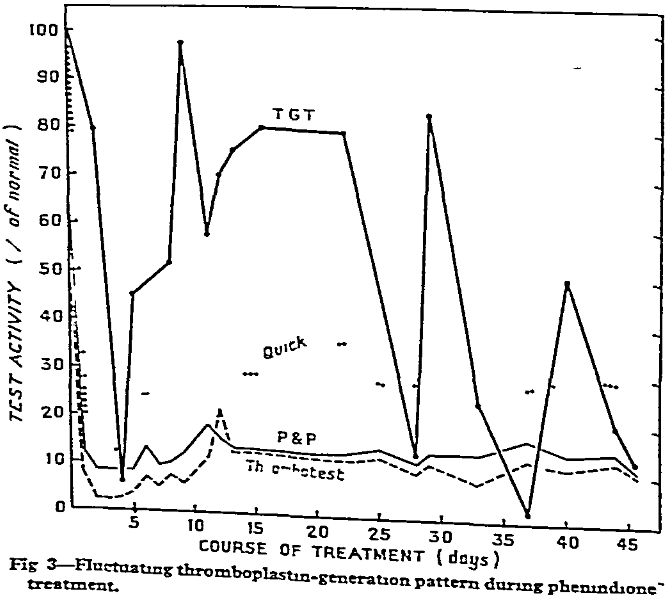

Fig 3—Fluctuating thromboplastin-generation pattern during phenindione treatment.

TABLE II—T G T PATTERNS IN PATIENTS TREATED WITH ANTICOAGULANTS

T G T pattern	Cases			
	Thrombotic	Doubtful thrombotic	Non-thrombotic	Angina
Fluctuating	13	2	0	5
Doubtful	3	1	1	0
Non fluctuating	11	7	0	0

test gave results below 100%, suggesting that thromboplastin generation was decreased

In six patients thromboplastin generation was depressed before anticoagulant treatment had been instituted Four of these showed depressed Quick prothrombin activity and a prolonged thrombotest, whereas only three gave a prolonged P & P test

In twenty-one patients the thromboplastin-generation test returned to normal or near normal during the course of phenindione treatment, although the Quick test was within the therapeutic range

The speed with which thromboplastin generation was depressed to 30% or less during phenindione treatment varied considerably In fig 4 the day on which such depression was first observed has been plotted for the whole series

Thrombotest and the Prediction of Hæmorrhage

Three non-fatal hæmorrhagic episodes arose during the course of treatment of the forty-three patients—two in group A and one in group B These incidents represent one non-fatal hæmorrhage per 8 months of short-term treatment On each occasion the Quick prothrombin activity was still within the therapeutic range, whereas the thrombotest was below 10%, and the thromboplastin generation less than 5% In the two patients of group A the P & P test was also less than 10% of normal

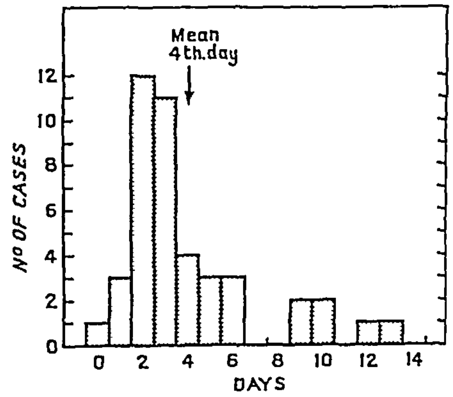

Fig 4—Days before thromboplastin generation was first observed below 30% of normal in forty-three patients on phenindione treatment

Death during Anticoagulant Treatment

There were four deaths—two in each group The numbers are too small for any conclusion to be drawn

Thromboembolic Complications

No thromboembolic episode was observed clinically in either group

Discussion

The Quick test, first described in 1935, has been the sheet anchor for the control of oral anticoagulants since their introduction nearly 20 years ago There have been many modifications of the test, but the basic principles have remained unchanged The main difficulty encountered has been the standardisation of the thromboplastin extracts Acetone-dried human brain, which has been prepared easily in our laboratory, has been found to give reproducible results Most modifications of the Quick test are sensitive to depressions of factor VII and prothrombin, which occur during treatment with oral anticoagulants The use of a powerful tissue-thromboplastin reagent in Quick's test makes it impossible to measure changes in factors involved in the production of intrinsic blood thromboplastin Several workers have shown that depression of thromboplastin generation also occurs during anticoagulant treatment (Biggs et al 1953, Hunter and Walker 1954, Koller 1954, 1955) Christmas factor and Prower-Stuart factor are involved in thromboplastin production, and both of these are reduced by the anticoagulants (Douglas 1955, Hougie et al 1957) Changes in Christmas factor are not measured by Quick's test

Our results relate to the Quick test performed with one particular type of thromboplastin reagent—i e, acetone-dried human brain—the same batch being used throughout the investigation Results with this batch were similar to those with previous batches we have prepared regularly over the past 13 years Commercial preparations are known to give variable results owing to variable degrees of factor-VII contamination (Verstraete et al 1957)

Hicks and Bonnin (1959) have suggested that, in the majority of patients, depression of thromboplastin generation by anticoagulants runs parallel with the depression of Quick's test, but they gave instances in which this relationship was not close In contrast, our results indicate that only in a minority is there good correlation between the two tests The Quick prothrombin time thus appears to be an incomplete measure of the anticoagulant effect produced by anticoagulants

Results with the P & P test and thrombotest were slightly better, but correlation was good in less than half the cases

Waaler (1957) showed that the P & P test was slightly sensitive to reduction in Christmas factor when low levels of factor VII and prothrombin had been attained From our investigations we gained the impression that the P & P test and thrombotest correlate well only when these extrinsic factors are considerably depressed

In the three cases having phenindione treatment, where there was spontaneous bleeding, the thrombotest indicated a dangerous depression of coagulability This is important since all three had seriously impaired thromboplastin generation, although the Quick prothrombin times were within the "therapeutic range"

In about *half* the patients a fluctuating pattern of thromboplastin generation could not obviously be related to the dosage of anticoagulant drug Such fluctuations do not seem to have been reported previously Their pattern is remarkably similar to the fluctuating coagulability pattern observed with heparin-plasma-clotting tests in patients with recent thrombosis who are not having anticoagulant drugs (Poller 1954, 1956)

Several workers have reported increased *thromboplastin* generation in patients with recent thrombosis (Poller 1957, MacDonald 1959, Spittel et al 1960) Thrombotest appears insensitive to such changes in contrast to heparin-clotting-time methods, which *may* register a thrombotic tendency The observation that the T G T was appreciably impaired in six cases before anticoagulant therapy was commenced is of interest In most of these cases there appeared to be a combined *defect* of coagulation factors, including prothrombin and associated factors

The day on which appreciable depression of thromboplastin generation was first registered was by *no means* constant, varying from the start of treatment to 13 days later This point has not been emphasised by previous workers, although impairment of intrinsic blood-thromboplastin generation, when the Quick prothrombin time was normal or only slightly prolonged, was observed by Koller (1954) and by Hunter and Walker (1954)

Our results suggest that the therapeutic ranges of the Quick test, the P & P method, and thrombotest are not directly comparable Either the accepted lower limit of 15% in the Quick test (using acetone-dried human brain as thromboplastin reagent) denotes too great a depression of clotting factors, or the lower limit of 10% with P & P or thrombotest is too high

Bjerkelund (1957) and other Scandinavian workers have employed the 10% lower limit, using the P & P method, for several years, with good results—i e , low incidence of complications From comparison of the Quick test and the P & P method, Smith and Schelling (1955) are of the opinion that the therapeutic range with the Quick test should be 34–48% prothrombin activity

Our results suggest that excessive reduction of thromboplastin factors may be an important factor predisposing to hæmorrhage In our series there were four cases of hæmorrhage, in three of these the results with P & P and thrombotest were *below* the therapeutic level of 10%, and the T G T showed thromboplastin generation to be below 5% of normal In contrast the Quick test showed the prothrombin activity to be in the therapeutic range—i e , above 15%—thus failing to give sufficient warning of possible hæmorrhage

It is as yet too early to define exactly the therapeutic limits with the thrombotest technique The similarity between P & P and thrombotest results suggest that the range will be 10–30%

The chief advantage of thrombotest is that it makes available to all laboratories a simple test which gives results as reliable as the more complicated P & P test On the other hand, there are disadvantages when it is compared with the Quick prothrombin-time test Amongst these are the greater care necessary in collecting blood specimens, and in preparing the glassware and syringes Although the siliconing of glassware appears simple, it is not without risks in unskilled hands Reconstitution of the freeze-dried thrombotest reagent requires great care One of the batches tested contained an agglutinin which gave agglutination similar to that obtained with human blood-group antibody, and this interfered with the reading of the end-point in some cases

Since more and more patients are being treated with anticoagulants, a great disadvantage is the high cost of imported thrombotest reagent Owren (1960) has shown that half quantities of the reagent give as reliable results and afford economy The general principles for preparing the reagent have been described (Owren 1959), but whether such an elegant and reliable lyophilised preparation would be obtained in a hospital laboratory remains to be seen The cost of a home-made preparation must also be appreciable If thrombotest does give some warning of possible hæmorrhages when in fact the Quick test does not, then there is a good case for introducing the newer test at the earliest opportunity In the meantime it seems advisable to keep the Quick prothrombin time between $1^{1}/_{2}$ and 2 times normal—i e , 30–20% prothrombin activity—where this established test is still being used For many years this plan has been adopted by one of us (H L), and it has proved satisfactory from the point of view of hæmorrhagic complications Toohey (1958) pointed out that the P & P method was superior to the Quick method for assessing dosage at the start of anticoagulant therapy, on the other hand, for outpatient long-term therapy, where specimens were taken at fairly long intervals, the Quick method was still reliable From our results with thrombotest similar conclusions may be drawn

Summary

Two groups of patients having anticoagulant therapy were studied

In group A, comprising thirty-one patients, anticoagulant dosage was based on Quick's prothrombin-time test, and simultaneous observations were made by Owren's thrombotest method, the prothrombin and proconvertin (P & P) method, and a thromboplastin-generation test

In group B, comprising twelve patients, anticoagulant dosage was based on Owren's thrombotest method, and simultaneous observations made by Quick's test and a thromboplastin-generation test

When group A patients were controlled by Quick's method about 30% of the simultaneous thrombotest results were below the therapeutic range, suggesting that too much anticoagulant was given

When group B patients were controlled by the thrombotest method about 30% of the simultaneous Quick test results were above the therapeutic range, suggesting that not enough anticoagulant was given

Among the forty-three patients there were three non-fatal hæmorrhages, and in each of these the Quick test results were within the therapeutic range whereas the thrombotest results were below the therapeutic range

Fluctuation of intrinsic thromboplastin factors was studied during treatment

Before the Quick test is replaced by the thrombotest in routine control of anticoagulant treatment more experience is required Meanwhile it is suggested that safer control will be obtained if the Quick prothrombin time, using the described acetone-dried brain extract, is kept at not more than twice normal, and the thrombotest at not more than 3 to $3^{1}/_{2}$ times normal No one-stage method is entirely safe in controlling anticoagulant treatment

We wish to express our thanks to the following members of the Department of Clinical Pathology, Manchester Royal Infirmary, who so ably assisted us in this investigation Miss Jean Carr, F I M L T , hæmatological technician, Dr M J Lewis, registrar in pathology, and Dr A L Buckley, resident clinical pathologist We also wish to thank Prof P A Owren for sending us preliminary information about thrombotest, and Messrs Nygaard & Co , of Oslo, for a generous supply of the reagent We are grateful to Evans Medical, Ltd , for augmenting our supplies of the reagent, and to Dr M C G Israels for his helpful criticism in the preparation of this paper

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CARDIAC ARREST
TREATED BY ELEVATION OF THE LIMBS FOR FIFTEEN SECONDS

W W WOODWARD
M B Sydney, F R C S, F R A C S

HONORARY SURGEON TO INPATIENTS, GENERAL HOSPITAL,
LAUNCESTON, TASMANIA

FILLING the arrested heart with blood from the patient's elevated limbs can restart beating, as I have already reported (Woodward 1952) The same observation was made by Fowler (1952), and the method has been used experimentally (Stephenson 1958) Blood can be transferred to the heart by gravity by raising the limbs vertically In states of reduced blood-volume, bandaging the limbs can help further, but experience has convinced me that, apart from this one indication, bandaging is unnecessary

On four occasions, I have confirmed the effectiveness of this method when the chest has been open [Launceston General Hospital numbers 77082, 81204, U R 7913, U R 14234], thoracotomy allowing direct observation of the heart while the limbs were raised In these four patients, mere elevation of the unbandaged limbs rapidly restored cardiac contractions Having seen these responses, I concluded that, provided two conditions are fulfilled, raising the limbs vertically before incising the *precordium* could be of value The provisos are (1) cardiac arrest has been immediately recognised, and (2) no more than fifteen seconds are spent in the manœuvre This method has been carried out on three occasions, and there has been no need for thoracotomy

Case-records

Case 1 —A B, aged 62, [U R 1781], on March 13, 1956, was given thiopentone and gallamine triethiodide intravenously for bronchoscopy During the operation, cardiac pulsation, seen through a bronchoscope in the left main bronchus, ceased The anæsthetist could not detect the radial or carotid pulses, and gave intratracheal oxygen under positive pressure, but without effect The patient's legs were *immediately* held vertically and, before the precordium could be incised, the heartbeat returned and the patient recovered consciousness

Case 2 —A C, aged 54, was admitted [U R 8358] on Dec 29, 1957, with severe hæmatemesis and melæna After eleven bottles of stored blood, he was still in coma but a direct transfusion was followed by sufficient improvement to allow operation When the stomach was opened, its wall did not bleed The aorta was palpated immediately there was no pulsation The patient's four limbs were immediately held vertically and, within fifteen seconds, the pulse returned After completion of partial gastrectomy, he recovered consciousness

Case 3 —A D, aged 61 was to undergo a left axillary dissection in St Vincent's Hospital, Launceston, on Sept 26, 1958 General anæsthesia was induced with thiopentone and gallamine triethiodide by Dr K S Goulston who soon after induction noticed absence of radial and carotid pulses, could hear no heart-sounds, nor measure the blood-pressure All visible parts of the skin became deathly pale and both pupils were widely dilated The theatre sister immediately held the legs vertical while her assistant did the same to the arms Oxygen was given, but it is well known (Stephenson 1958) that, though necessary, this is not effective alone Within fifteen seconds the pulse returned Operation was postponed, and the patient recovered consciousness Four days later the axillary dissection was performed without trouble

Summary

In rapidly recognised cardiac arrest, the pulse has been restored within fifteen seconds of raising the limbs into the upright position—on one occasion, the legs only, and at other times, all four limbs

Though cardiac massage is still the main method of treatment, it can at times be forestalled

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ACUTE FERROUS SULPHATE POISONING
TREATED WITH EDATHAMIL CALCIUM-DISODIUM

KENNETH SIMPSON
M D Lond, M R C P

ALAN BLUNT
M B, B Sc Birm, D C H, D Obst

From the Department of Child Health (University of Bristol), Bristol Royal Hospital for Sick Children

THE committee on toxicology of the American Medical Association (1959) advised the use of intravenous infusions of edathamil calcium-disodium (calcium disodium versenate) in the treatment of acute iron poisoning Since few reports have been published on the efficacy of this agent in acute iron poisoning we present the results obtained in a severe case

Case-record

A boy, aged 2, weighing 31½ lb (14 3 kg), was admitted two hours after swallowing about forty 5-grain (total amount 320 mg) tablets of ferrous sulphate He vomited an unknown number half an hour after taking them, and his stomach was later washed out at another hospital

On admission (10 40 A M, Feb 15, 1960), he was in severe shock and was unconscious The blood-pressure was too low to record Tetracycline was given intramuscularly, and an intravenous infusion of plasma was started at 11 A M Three-quarters of an hour later the radial pulse became palpable Edathamil 0 5 g in 400 ml plasma was given intravenously from 12 15 P M to 3 P M During the afternoon he passed several black fluid stools and vomited small amounts of blood The plasma-bicarbonate at 3 45 P M was 12 mEq per litre, and 80 ml *M* sodium lactate was given intravenously during the ensuing forty-eight hours From 7 P M on Feb 15 to 10 A M on Feb 16, 0 5 g of edathamil was given intravenously in 600 ml of 5% dextrose Consciousness gradually returned during Feb 16, and on the following day he began to take milk drinks The intravenous infusion was continued with 5% dextrose solution, and a third dose of 0 5 g of edathamil was given on Feb 17

During the night of Feb 17–18 he became increasingly restless, and by noon on Feb 18 was semiconscious, with acetonic breath and twitching limbs The liver on palpation was small and abnormally firm Blood-pressure, blood-glucose, and plasma-non-protein nitrogen levels were normal A diagnosis of hepatic coma was made, milk drinks were stopped, and tetracycline was given by mouth Plasma was substituted for 5% dextrose infusion The first of several electroencephalograms (E E G) was taken By Feb 19 clinical jaundice was evident, and, during the morning, four convulsions occurred Towards evening he became easier to arouse, by the next day he was fully conscious and beginning to play with toys From this point his recovery was rapid and sustained Clinical jaundice had disappeared, and the liver appeared normal in size by Feb 23

At follow-up on April 11 the child appeared to be in good mental and physical health and no abnormality was found on clinical examination Electrophoresis of plasma proteins, plasma thymol-turbidity, and thymol-flocculation tests were normal

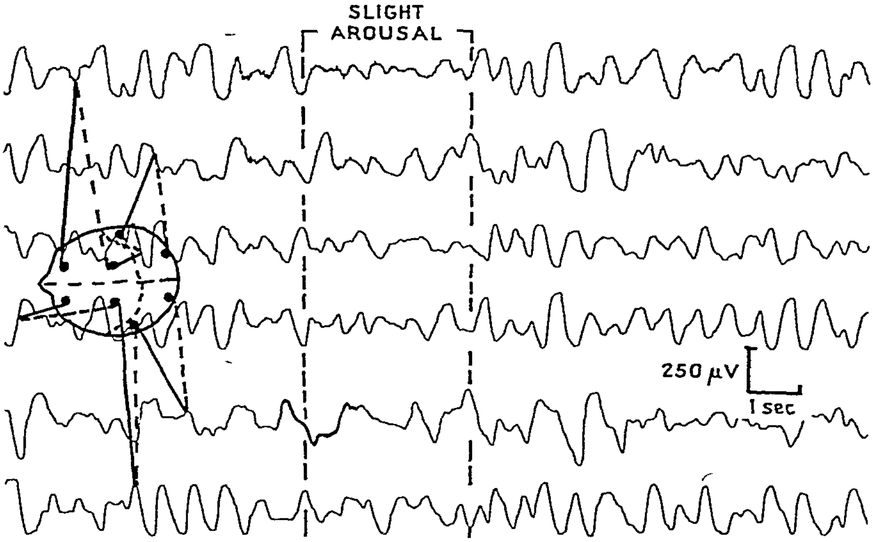

Fig 1—Electroencephalogram from a case of acute iron poisoning three days after admission.

Investigations

Serum-iron (µg per 100 ml by the method of Ramsay 1957)

Feb 15 12 15 P M	6260	Feb 16	4 30 P M	375
3 45 P M	1660	Feb 17	12 noon	314
6 45 P M	1000	Feb 18	9 30 A M	191
Feb 16 9 30 A.M	350	Feb 22	12 noon	105

Urinary iron —Urine was digested with nitric and perchloric acids as described by Collins and Diehl (1959) The iron content was then estimated by Ramsay's (1957) method

No urine was passed until 7 15 P M on Feb 15 From then until 5 P M on Feb 17, 761 ml urine, containing 5416 µg iron, was passed 3223 µg of this total was recovered between 7 15 P M and 11 15 P M on Feb 15

Serum transaminase (method of Reitman and Frankell [1957])

	Feb 15	*Feb 16*	*Feb 17*	*Feb 18*	*Feb 19*	*April 14*
Serum glutamic-oxaloacetic-transaminase	48	990	3400	2050	840	
serum glutamic-pyruvic-transaminase	25	700	2500	2400	1320	28

Other biochemical investigations —Total serum-bilirubin Feb 15, 0 25 mg per 100 ml , Feb 19, 4 1 mg Plasma-proteins Feb 15, 7 6 g per 100 ml , Feb 20, 4 9 g

Electroencephalography —Six E E G s were recorded The first, taken on Feb 18, was grossly pathological, showing large slow delta rhythms (1–2 cycles per second), up to 250 µV in amplitude, in all regions (fig 1) The patient was then comatose, but on one occasion, when he appeared to awaken spontaneously, the delta rhythms diminished considerably in amplitude for a few seconds The second record, taken a week later, when the patient was fully conscious though restless and irritable, showed a dramatic change The large delta rhythms had disappeared and there was very little rhythmic activity of any kind except for occasional runs of theta waves at 6–7 cycles per second (fig 2) Subsequent E E G showed a progressive return to normal, the last record, taken on March 3, being typical of the patient s age-group

Dr W Grey Walter thought the initial gross abnormality could have been due to direct specific neuronic intoxication, to a secondary disturbance of subcortical mechanisms as a result of hepatic dysfunction, or possibly to both

Discussion

In cases of acute iron poisoning by ingestion it is usually impossible to determine the amount absorbed because iron lost in vomit, gastric lavage, and bowel evacuations cannot be measured Serum-iron levels are usually regarded as indexes of iron transport, but they only indicate iron-content of the body within broad limits Experimentally, ferric iron dialyses slowly from serum even though iron-binding protein has been saturated (Laurell 1947) In ferrous sulphate poisoning, iron leaves the blood-stream rapidly, although probably present in ferric form (Reissmann et al 1955) Serum-iron levels in one of Spencer's cases (1951) fell from 3300 µg per 100 ml to 1120 µg in eleven hours In the case reported by Brown and Gray (1955), values fell from 5450 µg to 430 µg in thirty-nine hours

An estimate of total serum-iron based on the first determination made nearly four hours after the child took iron would be no more than a minimal approximation of the amount absorbed Assuming that his plasma-volume at the time was 5% of body-weight, the plasma-iron content was 44,100 µg In the fifty-three-hour period following the first serum-iron sampling, 5416 µg of iron, or 12% of the initial plasma-iron content, was recovered from the urine Of the iron excreted, three-fifths was found in the first urine passed after the initial edathamil infusion, but the second and third infusions were not followed by any rise in urinary iron excretion

Sunderman and Boerner (1949) quoted amounts ranging from 45 to 200 µg per twenty-four hours for normal urinary iron excretion The amount found in the urine of our patient represented a twelvefold increase of the maximum normal figure Increases in urinary iron excretion of the same order were found in hæmochromatosis (Figueroa et al 1955, Wishinsky et al 1955), hæmosiderosis (Greenwalt and Ayers 1955), and experimental iron poisoning (Foreman et al 1952), treated with chelating agents

Edathamil had little effect on the urinary iron excretion in our

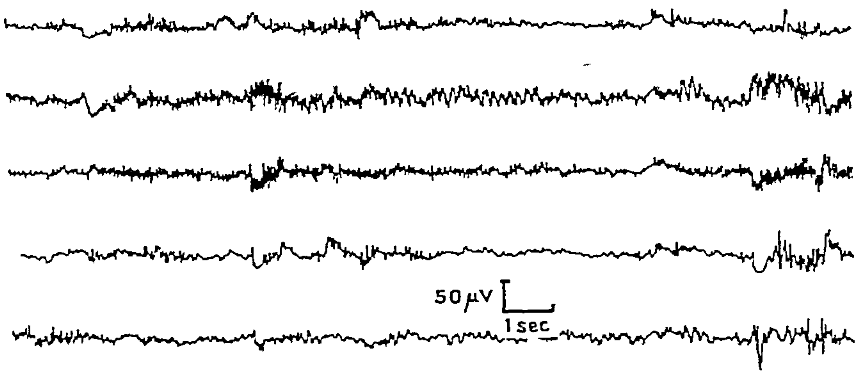

Fig 2—Electroencephalogram of same case seven days later

patient although serum-iron levels fell from 6260 µg per 100 ml to 1000 µg within seven hours If the drug increased diffusion of iron from the blood, it might be valuable in the first and most critical phase of iron intoxication in which shock with hæmoconcentration develops rapidly In rabbits poisoned with intravenous iron, shock developed within a few seconds (Brown and Gray 1955), it also appeared when animals were poisoned by intraduodenal instillation of iron in solution, a method which does not produce mucosal necrosis This evidence suggested that circulatory changes were a direct effect of excess iron in the vascular system If this were so, rapid removal of the excess might aid recovery from shock The rate of fall of serum-iron in our case did not appear to be faster than that recorded by Spencer (1951), whose case received no chelating agent Serum-iron levels in dogs poisoned with intraduodenal ferrous sulphate where higher in untreated animals than in those receiving edathamil intravenously immediately after iron was given (Bronson and Sisson 1960) Death was not prevented, however, and the amount of serum-iron did not appear to be the determining factor The only survivor was also given disodium orthophosphate into the stomach when iron was administered into the duodenum

The course of the child's illness followed closely the biphasic pattern emphasised by Prain (1949) and Spencer (1951) An initial period of shock, recovery from which could be attributed to the measures taken to increase plasma-volume and to correct acidosis, was followed about sixty hours later by a second period of coma The clinical diagnosis of hepatic coma was supported by very high levels of serum-transaminase, increased plasma-bilirubin values, changes in plasma-protein levels, and normal plasma-non-protein-nitrogen values The abnormal E E G records were also consistent with this diagnosis The second critical phase was successfully negotiated within forty-eight hours and recovery was then rapid The same sequence of events has been reported in severe cases which were not treated with chelating agents

Summary

A non-fatal case of acute iron poisoning in a boy, aged 2, is reported Treatment included the use of intravenous edathamil calcium-disodium (calcium disodium versenate), and its effect is discussed The plasma-iron content at the start of treatment was 44,000 µg In the following fifty-two hours 5416 µg of iron was found in the urine

The biphasic nature of the clinical course is again emphasised Relapse in our patient was the result of liver dysfunction

We are grateful to the consultant physicians of the department of child health and the department of pathology, United Bristol Hospitals, for their advice and their permission to publish this case

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CANCER OF THE ŒSOPHAGUS

PALLIATION BY INTUBATION

W P GREENING
F R C S
ASSISTANT CONSULTANT SURGEON

G S RAMSAY
M B Lond, F R C S
RESEARCH ASSISTANT

THE ROYAL MARSDEN HOSPITAL, FULHAM ROAD, LONDON, S W 3

THE most important function of any palliative procedure in cases of inoperable cancer of the œsophagus or of the cardia is the relief of dysphagia Obstruction in the œsophagus or the upper end of the stomach cannot always be relieved by radiotherapy, Souttar's tubes have certain disadvantages, and gastrostomy is a most undesirable procedure

Recently there has been a revival of interest in methods of inserting a tube through the obstruction, either via an œsophagoscope (Weisel et al 1959, Sachs 1959) or through a gastrostomy opening (Gourevitch 1959, Moghissi 1960)

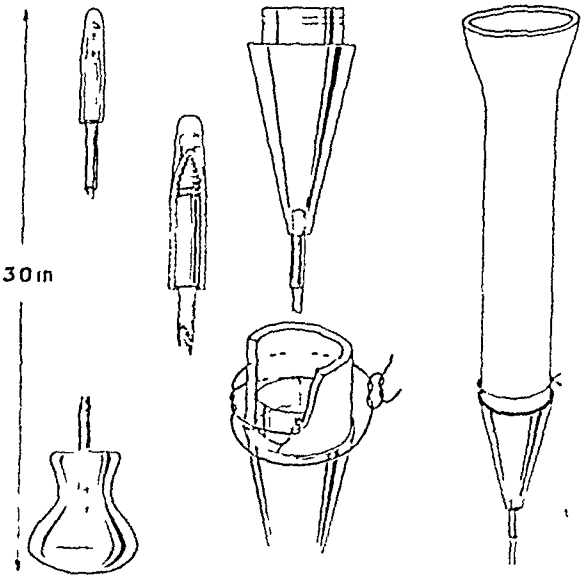
Ideally, after intubation, the patient should be able to swallow without difficulty, and there should be no restriction in the diet Gourevitch (1959) has summed up the main disadvantages of intubation through an œsophagoscope We would add another to his list—namely, the size of the tube that can be passed is limited by the diameter of the lumen of the œsophagoscope This is important because we believe that it is essential to insert as large a tube as possible, and this can only be done easily from below The danger of splitting the œsophagus, or of hæmorrhage from the growth, has been exaggerated, it is possible to dilate a malignant stricture much more widely than is generally believed

These points are important

1 The method should be simple Œsophagoscopy—particularly in the elderly patient—is not always either easy or safe

2 The tube should be of large diameter

3 The tube should be made of inert material, capable of being fashioned individually for each case, and available in different degrees of hardness to suit varying conditions



The œsophageal tube introducer

Over the past two years we have developed a method, used in 9 cases, which satisfies these requirements Polyvinyl chloride tubes, supplied in two degrees of hardness by Portland Plastics Limited, are used An introducer with interchangeable ends, to fit three different sizes of tube (numbers 30, 40, and 50), has been designed A flange is made at the upper end of the tube This can be done quite simply by immersing the end of the tube in boiling glycerin, at the temperature of which (290°C) it becomes easily malleable It is then passed over a conical object of suitable size, and, on cooling, the splayed-out end remains a permanent flange The introducer (see figure) consists of 30 in of Bowden cable with a screw-threaded end, to which can be attached either a small 'Perspex' tip, or one of three perspex cones The cable is coated with "cold-cure" 'Silastomer' (Midland Plastics Limited), this is a silicone rubber covering which is flexible and can be used at temperatures up to 200°C

Technique

The inoperability of the tumour is determined either clinically or at operation A high anterior gastrotomy is then made and the introducer, with the perspex tip attached, is passed up the œsophagus and delivered through the mouth by the anæsthetist The tip is then unscrewed and the appropriate cone attached These cones are so designed that the base fits into the lumen of the tube, while the rim of the cone, which is of slightly larger diameter than the outside diameter of the tube, does not project, and thus the tube cannot catch in the growth as it is pulled through The tube is tied to the base of the cone by a thread, passed through the wall of the tube and through the channel provided in the base of the cone Traction on the introducer then causes the tube to pass easily down the œsophagus, until the flange is just above the growth The cone is then detached, and any excess of tube cut off, so that the lower end lies in the upper third of the stomach The gastrotomy is closed

We wish to thank the department of medical physics at the Royal Marsden Hospital for making the instrument, and Midland Silicones Limited for the supply of "cold-cure" 'Silastomer'

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Preliminary Communication

BLOOD-CHOLESTEROL AND ASPIRIN

ARTERIOSCLEROSIS and cardiac infarction are particularly important problems at the present time Many workers consider that there is a definite relationship between the blood-cholesterol level and arteriosclerosis Various diets have been tried in arteriosclerotic diseases, and attempts made to lower the blood-cholesterol level by administering linoleic acid Dreyfuss [1] observed a rise in the blood-uric-acid level in some cases of arteriosclerosis, but emphasised that the blood-cholesterol level was not invariably raised I have noted that in some cases of arteriosclerosis not only the blood-cholesterol but also the blood-uric-acid level is raised

On the assumption that there might be a metabolic relationship betweeen cholesterolæmia and raised blood-uric-acid levels, an attempt was made to lower the blood-cholesterol level by decreasing the blood-uric-acid For this purpose small quantities of aspirin (1 5 g daily) were administered to 10 patients (6 men and 4 women) whose ages ranged from 38 to 65 years 6 of them had had myocardial infarction and 1 of these was also hypertensive, 2 were hypertensive, 1 had recurrent anginal pain, and 1 had peripheral arteriosclerosis

BLOOD-CHOLESTEROL AND BLOOD-URIC-ACID (MG PER 100 ML) BEFORE, DURING, AND AFTER TREATMENT WITH ASPIRIN 1 5 G DAILY

Case no	Before treatment		After 2 weeks treatment		After 1 month s treatment		After end of treatment	
	Chol-esterol	Uric acid	Chol-esterol	Uric acid	Chol-esterol	Uric acid	Chol-esterol	Uric acid
1	270	4 7	240	4 7	180	4 0		
2	370	6 2	220	6 2			370	
3	310	4 2	175	3 2	228	3 2		
4	330	5 2	286	5 0	230	6 0	310	6 2
5	270	4 0	230	5 0			300	4 2
6	350	4 8	280	4 0				
7	331	4 3	190	3 7				
8	240	5 0	198	4 35	215	5 4		
9	300	4 0	135	3 25				
10	342	4 5	260	4 7				

The effects on blood-cholesterol and uric-acid levels are summarised in the accompanying table

All these patients were treated while up and about, no change was made in their usual diet or in their daily routine After treatment with aspirin a striking fall in blood-cholesterol level, and a smaller fall in uric-acid level, was observed in all cases In several cases, blood-cholesterol levels rose after the cessation of treatment and reverted to their original value

I conclude that aspirin has an effect, so far unexplained, on the metabolism of cholesterol

Central Clinic
National Workers Sick Fund,
Tel Aviv, Israel

M EIDLITZ
M D Jerusalem

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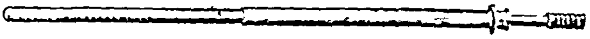
[1] Dreyfuss, F *Harefuah*, 1959, 57, 329

New Inventions

A SUCKER FOR EMPTYING THE INTESTINE

IN cases of small-bowel obstruction it is now the usual practice to empty the intestine at operation by means of a sucker The entire length can be cleared of fluid and gas by coaxing the instrument through successive loops of distended bowel

Because the available sucker ends are often too short to reach the whole length of small intestine, a special long sucker has been devised [1] for this purpose An alternative device, developed independently about the same time, has been made for me by Down Bros , Ltd , 21, St. Thomas' Street, London, S E 1



This sucker consists of a brass tube 6 in. long, with threads cut at each end so that it can be used to extend the standard Poole's sucker end by simply unscrewing the outer sheath and screwing in the extension tube, there is no need to extend the inner tube A $^1/_2$ in flange at the proximal end of the extension tube makes it easier to use

Guy's Hospital,
London. S E 1

REX LAWRIE
M.D , M S Lond., F.R.C.S , M.R.C.P

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[1] Savage, P T *Brit J Surg* 1960, 47, 643

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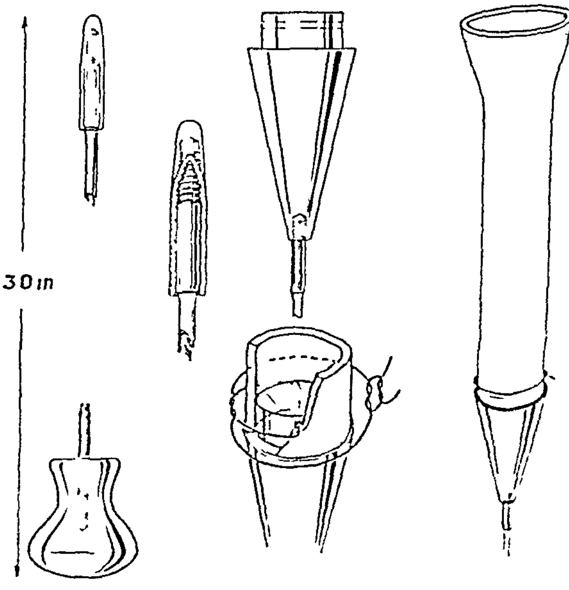

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Preliminary Communication

BLOOD-CHOLESTEROL AND ASPIRIN

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3	310	4 2	175	3 2	228	3 2		
4	330	5 2	286	5 0	230	6 0	310	6 2
5	270	4 0	230	5 0			300	4 2
6	350	4 8	280	4 0				
7	331	4 3	190	3 7				
8	240	5 0	198	4 35	215	5 4		
9	300	4 0	135	3 25				
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I conclude that aspirin has an effect, so far unexplained, on the metabolism of cholesterol

Central Clinic
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M EIDLITZ
M D Jerusalem

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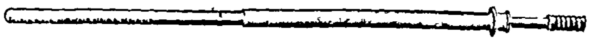
[1] Dreyfuss, F *Harefuah*, 1959, 57, 329

New Inventions

A SUCKER FOR EMPTYING THE INTESTINE

IN cases of small-bowel obstruction it is now the usual practice to empty the intestine at operation by means of a sucker The entire length can be cleared of fluid and gas by coaxing the instrument through successive loops of distended bowel

Because the available sucker ends are often too short to reach the whole length of small intestine, a special long sucker has been devised [1] for this purpose An alternative device, developed independently about the same time, has been made for me by Down Bros , Ltd , 21, St Thomas' Street, London, S E 1



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REX LAWRIE
M D , M S Lond., F R C S , M R C P

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[1] Savage, P T *Brit J Surg* 1960, 47, 643

patient although serum-iron levels fell from 6260 µg per 100 ml to 1000 µg within seven hours If the drug increased diffusion of iron from the blood, it might be valuable in the first and most critical phase of iron intoxication in which shock with hæmoconcentration develops rapidly In rabbits poisoned with intravenous iron, shock developed within a few seconds (Brown and Gray 1955), it also appeared when animals were poisoned by intraduodenal instillation of iron in solution, a method which does not produce mucosal necrosis This evidence suggested that circulatory changes were a direct effect of excess iron in the vascular system If this were so, rapid removal of the excess might aid recovery from shock The rate of fall of serum-iron in our case did not appear to be faster than that recorded by Spencer (1951), whose case received no chelating agent Serum-iron levels in dogs poisoned with intraduodenal ferrous sulphate where higher in untreated animals than in those receiving edathamil intravenously immediately after iron was given (Bronson and Sisson 1960) Death was not prevented, however, and the amount of serum-iron did not appear to be the determining factor The only survivor was also given disodium orthophosphate into the stomach when iron was administered into the duodenum

The course of the child's illness followed closely the biphasic pattern emphasised by Prain (1949) and Spencer (1951) An initial period of shock, recovery from which could be attributed to the measures taken to increase plasma-volume and to correct acidosis, was followed about sixty hours later by a second period of coma The clinical diagnosis of hepatic coma was supported by very high levels of serum-transaminase, increased plasma-bilirubin values, changes in plasma-protein levels, and normal plasma-non-protein-nitrogen values The abnormal E E G records were also consistent with this diagnosis The second critical phase was successfully negotiated within forty-eight hours and recovery was then rapid The same sequence of events has been reported in severe cases which were not treated with chelating agents

Summary

A non-fatal case of acute iron poisoning in a boy, aged 2, is reported Treatment included the use of intravenous edathamil calcium-disodium (calcium disodium versenate), and its effect is discussed The plasma-iron content at the start of treatment was 44,000 µg In the following fifty-two hours 5416 µg of iron was found in the urine

The biphasic nature of the clinical course is again emphasised Relapse in our patient was the result of liver dysfunction

We are grateful to the consultant physicians of the department of child health and the department of pathology, United Bristol Hospitals, for their advice and their permission to publish this case

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CANCER OF THE ŒSOPHAGUS

PALLIATION BY INTUBATION

W P Greening
F R C S
ASSISTANT CONSULTANT SURGEON

G S Ramsay
M B Lond, F R C S
RESEARCH ASSISTANT

THE ROYAL MARSDEN HOSPITAL, FULHAM ROAD, LONDON, S W 3

The most important function of any palliative procedure in cases of inoperable cancer of the œsophagus or of the cardia is the relief of dysphagia Obstruction in the œsophagus or the upper end of the stomach cannot always be relieved by radiotherapy, Souttar's tubes have certain disadvantages, and gastrostomy is a most undesirable procedure

Recently there has been a revival of interest in methods of inserting a tube through the obstruction, either via an œsophagoscope (Weisel et al 1959, Sachs 1959) or through a gastrostomy opening (Gourevitch 1959, Moghissi 1960)

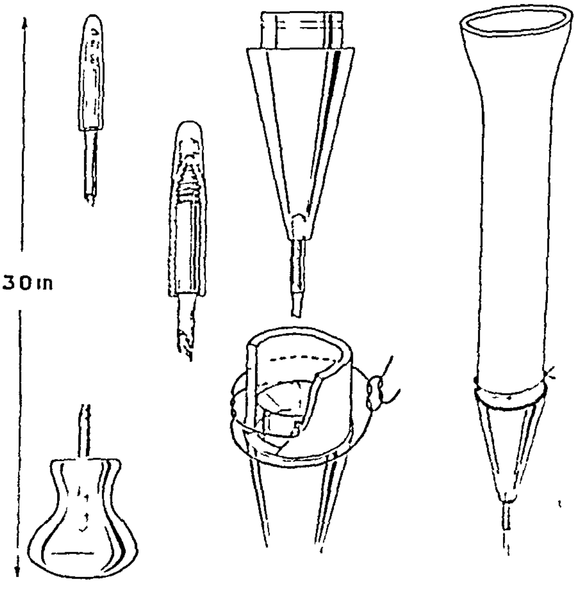
Ideally, after intubation, the patient should be able to swallow without difficulty, and there should be no restriction in the diet Gourevitch (1959) has summed up the main disadvantages of intubation through an œsophagoscope We would add another to his list—namely, the size of the tube that can be passed is limited by the diameter of the lumen of the œsophagoscope This is important because we believe that it is essential to insert as large a tube as possible, and this can only be done easily from below The danger of splitting the œsophagus, or of hæmorrhage from the growth, has been exaggerated, it is possible to dilate a malignant stricture much more widely than is generally believed

These points are important

1 The method should be simple Œsophagoscopy—particularly in the elderly patient—is not always either easy or safe

2 The tube should be of large diameter

3 The tube should be made of inert material, capable of being fashioned individually for each case, and available in different degrees of hardness to suit varying conditions



The œsophageal tube introducer

Over the past two years we have developed a method, used in 9 cases, which satisfies these requirements Polyvinyl chloride tubes, supplied in two degrees of hardness by Portland Plastics Limited, are used An introducer with interchangeable ends, to fit three different sizes of tube (numbers 30, 40, and 50), has been designed. A flange is made at the upper end of the tube This can be done quite simply by immersing the end of the tube in boiling glycerin, at the temperature of which (290°C) it becomes easily malleable It is then passed over a conical object of suitable size, and, on cooling, the splayed-out end remains a permanent flange The introducer (see figure) consists of 30 in of Bowden cable with a screw-threaded end, to which can be attached either a small 'Perspex' tip, or one of three perspex cones The cable is coated with "cold-cure" 'Silastomer' (Midland Plastics Limited), this is a silicone rubber covering which is flexible and can be used at temperatures up to 200°C

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The inoperability of the tumour is determined either clinically or at operation A high anterior gastrotomy is then made and the introducer, with the perspex tip attached, is passed up the œsophagus and delivered through the mouth by the anæsthetist The tip is then unscrewed and the appropriate cone attached These cones are so designed that the base fits into the lumen of the tube, while the rim of the cone, which is of slightly larger diameter than the outside diameter of the tube, does not project, and thus the tube cannot catch in the growth as it is pulled through The tube is tied to the base of the cone by a thread, passed through the wall of the tube and through the channel provided in the base of the cone Traction on the introducer then causes the tube to pass easily down the œsophagus, until the flange is just above the growth The cone is then detached, and any excess of tube cut off, so that the lower end lies in the upper third of the stomach The gastrotomy is closed

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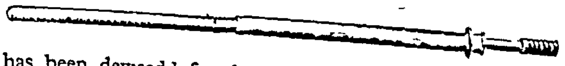

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[1] Savage, P T *Brit J Surg* 1960 47 649

Reviews of Books

Measurement of Subjective Responses

Quantitative Effect of Drugs HENRY K BEECHER, M D, Henry Isaiah Dorr professor of research in anæsthesia, Harvard University London and New York Oxford University Press 1960 Pp 494 102*s*

THE main problems of therapy are to relieve, and if possible abolish, pain and to ease anxiety, and there are age-old remedies for these conditions and brand-new ones hot from the chemist's bench The difficulty is to find the agents which work best and have the fewest disabling and harmful side-effects This is not easy since we have little knowledge of the physiological basis of anxiety, though we all think we mean the same thing when we use the word Again, we cannot describe pain nor compare one person's pain with that of another A good controlled experiment demands the use of dummy drugs, and this raises a question of ethics Should sufferers be given placebos? Dr Beecher points to the interesting fact that the worse a patient feels the more probable is it that a placebo will help him, which seems to show that pain and anxiety render patients more suggestible Placebos may even induce undesirable side-effects As far as relief of pain is concerned it is possible that few drugs relieve the pain itself, but many lessen the reaction to pain, and it is the reaction which is distressing, as the response of people who have undergone frontal leucotomy or lobotomy illustrates Pain, like all perceptions, is not pure, but contaminated by the reaction component, and it is this rather than the pain per se which differs so much from person to person, or in the same person in different conditions

This last point raises the question of the usefulness of experimental as against clinical assays of pain-relieving drugs In experimental conditions the human subject suffers little anxiety, he knows that the trauma is transitory and unimportant He is, therefore, a bad experimental animal On the other hand, the use of animals yields results which are clinically useful since to the animal the experimental threat is as great as any other and holds the same elements of anxiety Thus, the animal and the sick man hold remarkably similar views on the efficacy of certain drugs These are some of the facts discussed by Dr Beecher He has planned a number of ways in which errors of assay can be avoided and imponderables measured to some extent He deals with pain- and anxiety-relieving substances, and a number of others affecting nausea, pruritus, cough, euphoria, sedation, and so on He makes the interesting statement that many cough-suppressing drugs do not really reduce the frequency of cough but do reduce the patient's awareness of it Clearly this is an important and interesting book, well worth study, especially since the methods advocated can be used for measurement of reactions, quite apart from the effect of drugs on the causes of the reactions

The Neurological Examination of the Infant

ANDRE-THOMAS, YVES CHESNI, S SAINT-ANNE DARGASSIES Editors R C MAC KEITH P E POLANI, E CLAYTON-JONES London National Spastics Society 1960 Pp 50 5*s*

THIS concise, informative, and well-produced guide to the neurological examination of the infant is published as a hard-cover supplement to the *Cerebral Palsy Bulletin* Pædiatricians and others will be grateful for the information in this handy but durable volume because it is not readily accessible elsewhere although essential for the acquirement of the important skills required

The first part which deals with the neurological examination of the newborn, is based on a regional scheme which enables the examination to be carried out in a methodical well-organised way This is described with great clarity both in words and in diagrams The second part is concerned with the examination of older infants and has perforce to consider the evolution of each function separately This makes it less helpful as a technical handbook, and in spite of the inherent dangers it might have been useful to include a chronological table synthesising the approximate neurological
expected at appropriate months during the first yea

Medical Physiology and Biochemistry

Howell's Textbook of Physiology 18th ed Editors Th
RUCH, PH D, professor and executive officer, depa
physiology and biophysics, University of Washington
Medicine, the late JOHN F FULTON, M D, Sterling
of the history of medicine, Yale University School of
Philadelphia and London W B Saunders 1960 Pp 1

THIS is an excellent edition of an old textbook, und
name and with an additional editor The title atte
summarise the aims of the book—namely, to give an acc
physiology which is firmly based on the fundamental sc
and to show how it relates to clinical problems of a s
nervous, or psychiatric kind The editors have had adr
help from an array of workers each of whom is well kn
his own territory The writing is clear and the infor
accurate Discussion of the clinical applications has
woven successfully into the general text and not
separately as though clinical and scientific physiology
things apart Many chapters have been entirely rew
and the others drastically revised Purely biochemical m
has been omitted At the beginning of each chapter there
useful summary of its contents, and at the end of each a nun
of references is given This edition is a great improvemen
its immediate predecessors in that the index is full
informative so that the book can be used without difficult

Publishers face enormous difficulties in keeping down
price of a new book, particularly one which must have m
clear figures, and few of those for whom this book is writte
medical students—will feel able to buy it We may have
return to the days when books were so costly that they w
chained, and lecturers revert to their original task of reading
those who sit under them

The Urological Aspects of Bilharziasis in Rhodesia

R M HONEY, M B, F R C S, consultant urologist, Salisb
Hospitals Group, Rhodesia, M GELFAND, C B E, M D, F R C
consultant physician, European and African Hospitals, Salisbu
Rhodesia Edinburgh E & S Livingstone 1960 Pp
7*s* 6*d*

FROM a study of 300 European and 100 African cases,
authors of this valuable book define a number of import
differences from the more widely known Egyptian form of
disease and draw attention to its varied manifestations in wh
and coloured races The disease is so endemic among Afric
that the early symptoms are often disregarded and advice
sought only in the later stages On the other hand, the a
incidence among Europeans at the time of diagnosis is consid
ably lower This difference may in part account for the f
that no cases of carcinoma in association with bilharziasis w
encountered among Europeans although in Africans they w
not uncommon Neither race, however, seems particula
prone to secondary urinary calculi The cystoscopic appe
ances and radiological findings in various phases of the dise
are discussed in detail and amplified by a number of w
chosen illustrations

In the matter of treatment the authors emphasise the valu
pyelography in conjunction with instrumental examinatio
distinguishing between the effects of ureteric obstructio
reflux and in determining the appropri
complications in the upper urinary tract

Stress and Psychiatric Disorder

Scientific Publications 1960 Pp 15
papers read and discussed at the se
the Mental Health Research Fun
stimulating survey of modern rese
on men and animals The pape
under stress in children (E J Ant
in animals (Howard S Liddell),
of psychiatric reactions to stre
Sutherland) deserve special me
Tanner, secretary of the res

THE LANCET

LONDON 19 NOVEMBER 1960

New Ideas on Epidemic Virus Infections

MANY of the important epidemic virus diseases of man are transmitted directly from person to person without the intervention of an intermediate or alternate host. Of the factors which influence susceptibility, such as inherent or acquired immunity, some are quite well understood, but the factors affecting virus transmission are much less well defined. Even in such a well-studied disease as poliomyelitis it is uncertain whether virus from the throat or from the fæces is the more important. In many respiratory infections infected secretions are probably the source of the virus, but we do not really know exactly how and where the virus reaches its next host. We would expect to find that such virus infections are more readily transmitted when people live under crowded conditions, and when standards of hygiene are low, and this seems to be true for poliomyelitis and the common acute respiratory virus infections. It is well known, however, that some virus diseases tend to become epidemic in the summer and others in the winter.

ANDREWES[1] has pointed out that, although Asian influenza was seeded widely in many countries by modern means of travel, yet in most places epidemics developed only when the cold season came on. Temperature could not determine the "winter factor", for otherwise "the tropics would never get epidemics at all", and he suggested that in winter the main change was that people were more crowded where they lived and worked—a change which applies particularly to children who go back to school in the autumn, and who often get colds then. HOPE-SIMPSON[2] found an astonishingly close correspondence between increase of outdoor temperature and decrease in the number of patients who consulted him on account of colds. In another study he showed over a three-year period in a group of volunteers that there was a similar correlation between the appearance of symptoms of colds and decrease of temperature 1 ft. below the surface of the earth. He suggested that the reason for these correlations is that in cold weather we heat our rooms and thus reduce the relative humidity of the air, and he found that switching on a one-bar electric fire in an average-size room with the window and door open reduced the relative humidity from over 80% to about 50% as the temperature rose from 20° to 30°C. This drier air, by drying the mucous membranes of the respiratory tract, may increase susceptibility to infection. WADDY[3] earlier proposed that low absolute humidity could act in this way to aid the spread of airborne disease, and one of the illustrations he used to support his view was the influenza pandemic of 1918–19. Nevertheless, when volunteers are inoculated with cold viruses at a wide range of humidities and temperatures the frequency with which colds develop does not seem to vary.[4 5]

Polioviruses, by contrast, are more prevalent in the later summer months, and the explanations of this have run on the same lines as those of changes in the prevalence of other infectious agents found in the fæces—i.e., greater frequency of fæcal-feeding flies, and the larger consumption of uncooked food. These factors must be assumed to overcome the effect of larger amounts of light and higher temperatures, which would tend to reduce the amount of surviving virus. Humidity is not generally regarded as an important influence on the transmission of polioviruses.

Laboratory experiments by HEMMES et al.[6] in Utrecht may cause us to revise our thinking, and may reconcile some apparent conflicts. These workers prepared from virus suspensions aerosols which they held in a closed system, measuring the rate at which virus infectivity was lost. Temperature and absolute humidity had little effect on this rate, but it was strongly influenced by relative humidity, and there seemed to be a sharp distinction between results obtained at a relative humidity of 40% or lower and one of 50% or higher. In the case of influenza virus (PR8 strain) inactivation of infectivity was slow in the drier conditions and over 10 times more rapid in the moister conditions. The reverse held for a strain of poliovirus type 1, which survived well at relative humidities above 50%, but which at 40% or lower was inactivated so quickly that no virus could be recovered from an aerosol 30 seconds after spraying. Experiments of this sort have many technical snags: some of the aerosol may be lost on the wall of the container, and the composition of the suspending medium or the medium in which samples were collected may greatly affect the survival of viruses. But it is very unlikely that such technical difficulties would alter the relatively greater rate of inactivation of influenza virus in humid air and of poliomyelitis in drier air. In fact the observations with influenza have been confirmed independently[7] in experiments conducted by a somewhat different technique. HEMMES et al. point to the correlation between low indoor relative humidity and increased prevalence of influenza, and between high indoor humidity and increased prevalence of poliomyelitis. Their calculations suggest that in the colder months the relative humidity indoors drops below the critical zone of 40–50% which was found in their experiments. Their hypothesis, then, is that seasonal variations in the prevalence of these two virus infections result from variations in the relative humidity indoors, which in turn affect the chances of survival of the viruses in the dried state

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[1] Andrewes C H *J roy Soc Hlth* 1958 78 533

[2] Hope-Simpson R E *ibid* p 593

[3] Waddy B B *Lancet* 1952 ii 674

[4] Andrewes C H *ibid* 1949 i 71

[5] Dowling H F Jackson G G Spiesman I G Inouye T *Amer J Hyg* 1958 66 59

[6] Hemmes J H Winkler K C Kool S M *Nature Lond* 1960 188, 430

[7] Harper G L Unpublished.

This hypothesis has the great virtue that it can be readily tested Many different viruses are now known to cause respiratory disease in winter, while many other members of the enterovirus group tend, like polioviruses, to be found in summer It should not be difficult to compare the survival of some of these viruses at high and low relative humidities with the known facts of their epidemiology, and thus to substantiate or refute this interesting suggestion

Endocrine Exophthalmos

THE exophthalmos associated with Graves' disease is commonly of minor importance compared with the thyrotoxicosis it is usually mild and rarely accompanied by paralysis of the external ocular muscles By contrast, in the exophthalmos associated with exophthalmic ophthalmoplegia,[1] thyrotoxicosis is usually mild or has been relieved by treatment or replaced by frank myxœdema, but the paralysis of external ocular muscles is often pronounced and may become complete and vision may be jeopardised by secondary infection or vascular thrombosis These two clinically different types have been termed thyrotoxic and thyrotrophic exophthalmos respectively, implying that the former results from increased secretion of thyroid hormone and the latter from increased secretion of thyroid-stimulating hormone (T S H) These terms are wholly misleading since every gradation between the two syndromes can be found, the pathological anatomy is essentially the same, and there is no evidence that increased secretion of either the thyroid hormone or T S H plays a major part There is, however, experimental evidence that exophthalmos is produced more easily in the hypothyroid animal[2]—an observation which may be relevant to the severity of eye signs in exophthalmic ophthalmoplegia and their mildness in Graves' disease

The principal agent responsible for experimental proptosis was found to be present in extracts of pituitary tissue,[3] [4] and in 1953 Dobyns and Steelman[5] separated the exophthalmos-producing substance (E P S) from T S H by differential solubility in trichloracetic acid They tested it by its capacity to produce exophthalmos in the minnow, *Fundulus heteroclitus* Clinical evidence in support of the experimental work has been accumulating In 1956 two groups[6] [7] described their work on the measurement of T S H in serum in a total of 35 patients with thyrotoxicosis or exophthalmic ophthalmoplegia They used different techniques, and their results at best were only semiquantitative Both groups were generally able to detect T S H in the serum of their patients one[6] found no correlation with the degree of exophthalmos, while the other[7] found some evidence suggesting that T S H might occasionally be increased with severe exophthalmos Adams and Purves[8] pointed out that T S H is normally present in high concentration in the serum of patients with myxœdema and that it is suppressed by treatment with thyroid hormone They suggested that the presence of normal amounts in the serum of thyrotoxic patients is surprising and may indicate a failure in the mechanism for its suppression—a failure that may be the cause of Graves' disease There is no good evidence, however, that T S H is the cause of exophthalmos

In 1954 Dobyns and Wilson,[9] using the minnow, demonstrated E P S in the serum of 6 patients with exophthalmos and suggested that the degree of response in the fish was correlated with the severity of the exophthalmos This work has been extended by McGill[10] using the goldfish, *Carassium auratus*, and by der Kinderen et al[11] using the carp, *Cyprinus carpio* Both groups developed reasonably satisfactory quantitative procedures and found evidence suggesting that the active principle causing exophthalmos was the same in serum and in pituitary extracts They both examined the serum from a large series of people and detected an abnormally high level in patients with progressing exophthalmos, a normal level in those with stationary or regressing exophthalmos or with myxœdema, and a low level in those with pituitary failure There is therefore clinical evidence to support the claim that exophthalmos is caused by increased secretion of E P S

Rundle and Pochin[12] and Dobyns[13] showed that protrusion of the eyeball is the result of an increase in the bulk of the retrobulbar tissues The amount of fat in the fat depots is much increased, and the extraocular muscles are greatly enlarged and their fat content may be doubled Dobyns claimed that in the laboratory animal the fat is unusually gelatinous and is infiltrated with leucocytes, lymphocytes, and tissue macrophages, and the amount of fat in the muscles is closely correlated with muscular weakness Similar but less severe changes may affect skeletal and cardiac muscle, and large amounts of fat are found in the liver, kidneys, and epithelium besides large phagocytic cells in the lungs, spleen, and lymphnodes Evidently the effect of E P S is widespread, and indeed it is highly improbable that the pituitary gland would produce a hormone which specifically caused exophthalmos It is more likely, as McGill suggests, to be a general metabolic hormone, possibly influencing water partition in fat deposits, and giving rise to ocular protrusion only when secreted in excess

The treatment of endocrine exophthalmos has been reviewed by Brain[14] No specific endocrine therapy has been proved to be uniformly effective Œstrogens and thyroid extract have been tried extensively, but

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1 Brain W R *Lancet*, 1936 i 182
2 Marine D Rosen S H *Amer J med Sci* 1934 188 565
3 Loeb L Friedman H *Proc Soc exp Biol N Y* 1931 29, 648
4 Shockaert J A *ibid* p 306
5 Dobyns B M Steelman S L *Endocrinology* 1953 52, 705
6 Querido A Lameyer L D J *Proc R Soc Med* 1956 49 209
7 Gilliland I C *ibid* p 212
8 Adams, D D Purves H D *Metabolism* 1957 6 26
9 Dobyns B M Wilson L A *J clin Endocrin* 1954, 14 1393
10 McGill, D A *Quart J Med* 1960 29 423
11 der Kinderen P J Houtstra Lanz M Schwarz, F *J clin Endocrin* 1960 20 712
12 Rundle F F Pochin E E *Clin Sci* 1944 5 51
13 Dobyns B M *Surg Gynec Obstet* 1946 82, 609
14 Brain W R *Lancet* 1959, i 109

there is neither physiological nor clinical evidence to suggest that these will suppress the secretion of E P S Irradiation of the pituitary gland is the most logical treatment and appears to be effective in some cases, but in general the suppression of any pituitary secretion by irradiation tends to be slight and transient, as is shown by experience of this method in Cushing's syndrome. Irradiation of the orbits has its advocates, but it is difficult to establish that any improvement is not the result of accidental irradiation of the pituitary gland. Hypophysectomy or section of the pituitary stalk is apparently very effective, but is drastic[15], and, for the present, the most reliable treatment for severe cases is tarsorrhaphy or orbital decompression.

Bathing-water

IN this climate bathing is an unnatural habit and it may be for this reason that so many ills have been attributed to it. Warnings of the danger of immersion after meals, in convalescence, or when drenched with sweat are commonplaces of our folk medicine. The published evidence of infections after bathing is slight and not always convincing, but it is reasonable to distinguish between bathing in a modern swimming-bath and in natural waters fouled by unknown concentrations of human and animal excreta from all orifices The water in a swimming bath circulates continually through a filtration and chlorination plant. It can be polluted by no-one except the bathers and, though the degree of chlorination recommended by the Ministry of Health is not immediately bactericidal, the level of bacterial contamination is kept low

It is possible that Weil's disease, to which Dr BREEN[16] has called attention, is the gravest danger to which the bather in natural waters is exposed. Its milder manifestations may escape diagnosis in its more severe forms it is still often fatal. It is not a notifiable disease, but unofficial figures suggest that its incidence in England and Wales is about the same as that of typhoid fever but that its fatality-rate is higher The leptospiræ (presumably derived from the urine of rats) can survive in water for at least a matter of hours, and experience suggests that the limpid Test is as dangerous as a source of infection as the stagnant water in an old gravel pit. Traditionally infection is most common in those who work in sewers, fishmarkets, and surface coal diggings, but today agricultural labourers are infected as frequently as any other group It would therefore be unwise to think that bathing is the only source of infection or that, because a patient has bathed, the source of his infection is established.

Tubercle bacilli survive the ordinary processes of sewage purification and can be detected in many effluents A few cases of tuberculosis in children have been attributed with some reason to immersion by design or accident in fresh water[17-19] There may, of course, have been other sources of infection but in every case the bathing site was heavily contaminated with sewage containing tubercle bacilli—and we know that the dose of tubercle bacilli needed to produce a primary infection is very small. There are other reasons too—e.g , the danger of rendering cattle who drink the water sensitive to tuberculin—which make it important that the effluents from sanatoria should be free from viable bacteria, and perhaps this has not had the attention it deserves

Many sewage effluents contain salmonellæ. and a good deal of raw sewage and farm drainage enters our rivers without any treatment at all The water in all our larger rivers is in fact diluted sewage, and why salmonella infections are not frequent among bathers no-one really knows Isolated infections will seldom be reported, but not more than a dozen small epidemics have been recorded[20] The sewage is of course diluted, but the flow of water is at its least when bathing is popular Salmonellæ disappear rapidly from seawater by what we must in our ignorance call " natural agencies " It may be that fresh water teeming with animal and plant life can be equally fatal Possibly modern methods of isolating bacteria from water are so effective that they exaggerate the danger (the minimum infectious dose of many salmonellæ is 10^5 organisms or more) there is at least a hint of this in Dr BOYCOTT's findings.[21] Some quantitative estimation of salmonellæ in rivers might help to elucidate this problem There are other infections which might, in theory, be acquired by bathing Some of the earlier work on poliomyelitis in the U S.A. suggested an association between that disease and bathing in rural areas, but other contributory factors such as fatigue could not be excluded. Today we might suspect that other enteroviruses could be spread in this way In general, however, no association between bathing and infectious disease is so obvious as the other hazards—sunburn, traumatic damage of all kinds, and drowning Far too many people in this country cannot swim, and it would be a pity if they never learnt because of a theoretical danger of infection.

Bacteriological standards of purity can be applied to drinking-water because its composition is more or less constant. Weather such as we have been enjoying will alter the flow of a river manyfold within a few hours and bring down silt, sewage, and dead cats in unforeseeable amounts To make bathing safer we must use cruder methods The main danger probably comes from the discharge of human sewage. The river boards and local authorities do their best to minimise its effects, but the work is slow and costly Bathers in turn will do well to eschew the reaches immediately below the outfalls—if they know where these are. The council of the Society of Medical Officers of Health has been considering this problem, and has been forced to admit that it can offer no remedy other than a general clean-up They add that their members will be unwise to press for these measures on the grounds of health We are sure they are right the boundaries between public health and amenity are ill defined.

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[15] McCullagh E P Clamen M Gardner W J *J clin. Endocrin.* 1957 17 1277
[16] Breen G E *Lancet*, Sept. 17 1950 p 619
[17] Gaustad, V *Acta tuberc. scand.* 1947 21 281
[18] Sennel P *ibid* 1950 24 357
[19] Miller F J W, Anderson, J P *Arch. Dis Childh* 1954 29 152.
[20] Moore B *Bull Hyg* 1954 29 689
[21] Boycott J A *Lancet*, Oct. 1, 1960 p 760

Annotations

WORKING WIVES—AND THEIR CHILDREN

THE shortage of teachers, nurses, and social workers is causing alarm and despondency Each year there are fewer unmarried women, and nearly all of them already have jobs If more women are to be found to fill the empty posts, they will be married women Many hospitals now employ married nurses part-time, and efforts are being made under the Ministry of Education to find means of persuading married women teachers to return to their profession

On Nov 10 a conference was held by the National Society of Children's Nurseries entitled "Working Wives—What of the Children?" Dr Viola Klein pointed out that, though the number of married women in employment is increasing, only a small proportion of them have young children More than half the women in employment today have no children under the age of 16, the 1951 census showed that of the households which had children under 16, two-thirds had no child under school age, and, since the average family nowadays has less than three children, most women spend only a few years with very small children, and by the time they are 35 (or 40 at the latest) they are relatively free The popular image of the doting mother and her two small children is unrealistic, said Dr Klein, and seldom found Moreover, despite increasing concern and discussion about mothers going out to work, the mother who does nothing but look after her children is in fact a new phenomenon She is not to be found in agricultural communities In the mid-19th century one married woman in every four had a job, moreover she had on an average 6 children and worked long hours under appalling conditions Nowadays one married woman in three has a job, but more than half of these have no child under the age of 16

Several speakers pointed out that we do not yet know whether the regular absence of the mother for part of the day does any harm to the child Though working mothers are commonly blamed for juvenile delinquency, evidence is scanty, and there is no evidence at all that the effects of daily separation are comparable to the proven ill effects of total separation and deprivation [1]

Dr Lumsden Walker thought that whether a woman with young children should go out to work is an individual matter Some women, unable to stand almost total isolation with young children, make better mothers if they do go out for at least part of each day Factors which encourage a woman to go out to work are the modern small houses and labour-saving devices, increasing urbanisation with few social contacts, small families, and (in some areas) social pressures, particularly towards the purchase of "advantages"—i e, consumer goods Against mothers going out to work are different kinds of social pressures, and a strong and widespread feeling of guilt, often induced by "the mess of popular psychological teaching" which creates problems such as "anxiety about separation-anxiety" Also important are the attitudes of husbands and in-laws, and the availability of work

There seemed to be general agreement that the mental health and the happiness of the coming generation depends on the love and security of maternal care, but opinions differ on what constitutes this Many people believe, with Dr Lumsden Walker, that stable happy parents can do more or less what they like without injuring their children's psyches, but that the situation is very different where there is instability Anxiety and depression are probably commoner among women today than ever before, and many think that one reason for this is the social isolation of women that is characteristic of modern society A woman has lost her previous functions as helpmate to her husband in breadwinning and as chief educator to a large brood of children, yet society imposes no demands that she seek substitute functions She can try her hand at a paid job or at social welfare activity, but usually nobody says that she must And so the modern wife, after her youngest child has started school, is partly functionless, which means that she is likely to question her very reason for existence and to feel a vague but pervasive dissatisfaction [2] She may try to compensate for her own troubles with the aid of her child, but the effects of overprotection on the child are well known [3–6]

If a mother of young children who wants to go out to work is to be either encouraged or helped, provision must be made for the children At present, however, there are only 79 day nurseries open in the whole of London, and most of the places in them are reserved for children whose mothers are the sole breadwinners in the family Indeed, in the whole of this country there are no more than a few places for children whose mothers work because they want to or because they feel a need to spend part of the day away from home On the other hand, at least one local authority has now given priority to the children of women teachers, so that their mothers, much needed, can return to their profession, and in our correspondence columns this week Dr Coghill speaks of the West Middlesex Hospital's plans for a creche-cum-nursery-school for the children of married nurses

But there is more to the problem than this To work full-time and also look after a house and family requires a good deal of organisation, and also stamina, both physical and mental Naturally many women prefer to work part-time, and it has been shown [7] that wherever part-time work is to be had there is a supply of suitable workers Many employers, however, are reluctant to employ part-timers, because these increase their administrative burden, along with compulsory contribution to insurance schemes Moreover, absenteeism is much higher in women than in men, largely because women must stay at home not only for illness in themselves but also for illness in their families [8]

From the standpoint of the mother, an important point is that, if she does not continue to work while her children are young, she may lose the ability to do so, and continue to be housebound and probably frustrated when her children become independent of her In many skilled occupations and professions, including our own, failure to practise leads to loss of skill Moreover in many professions, if one stops working, one drops out of everything few posts are open to a woman doctor who has not practised for ten or twenty years Lastly, even if a woman retains or regains her skill and has a chance of a suitable job, she may still lack self-confidence. A woman who has been tied to the household for many years may find that she has an insuperable psychological block against returning to work in the outside world. Such a block is often seen in just those women who seem most frustrated by the isolation and semi-idleness of their home lives, and therefore might gain most from work.

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[1] Bowlby J Maternal Care and Mental Health World Health Organisation 1951

[2] Rose A M Mental Health and Mental Disorder London, 1956

[3] de Leeuw, H Woman the Dominant Sex London 1957

[4] Levy D M Maternal Overprotection New York 1943

[5] Strecker E Their Mother's Sons Philadelphia 1946

[6] Wylie P Generation of Vipers London 1955

[7] Myrdal A Klein V Women's Two Roles London 1956

[8] Medical Research Council Industrial Health Research Board Hours of Work Lost Time, and Labour Wastage (Emergency Report no 2 H M Stationery Office 1942) A Study of Absenteeism among Women (Emergency Report no 4 H M Stationery Office 1943) A Study of Certified Sickness Absence among Women in Industry (Report no 86, H M Stationery Office 1945)

There are many possible ways of helping to get over these difficulties. In the first place, those who advise young girls on the choice of training would do well to bear them in mind. Later, women whose children are grown up can be encouraged to use their training and experience, to revise their knowledge and practise their skills, or else to take up new training, and this would save some mothers from going out to work while their children are very young. Any drive to induce professional women to return to work would be more successful if it were accompanied by income-tax concessions: many more women would work if the cost of mother-substitutes were regarded as a legitimate expense.[9] Ashley Montagu has suggested[9] that women should have maternity leave, lasting two years, and also that married people of both sexes should work for only four hours a day. On a more immediate level, extension of the home-help system might help more women to work part-time, and, by raising the status of the domestic workers themselves, it would induce more women to take up this occupation.

These suggestions concern a number of individuals who seem to need them, and they receive publicity because society badly wants certain types of women workers. But what is even more necessary in the long run is research into the needs of women and their husbands and children.

TUMOUR VIRUSES

AT present, with the possible exception of warts, there is no known tumour virus in man, but, tumour viruses being widespread in other animals, it seems unlikely that man is in truth thus exceptional.[10] Toolan et al.[11] have described the isolation of a virus which causes a distinctive disease in hamsters inoculated as newborns or in utero (within a week before birth). The disease manifests itself in deformities consisting of small size, flattened foreface, or microcephalic domed head, protruding eyes and tongue, absent or abnormal teeth, and fragile bone structure. These deformities, previously described by Toolan[12] in her original account of the isolation of the virus, are now thought to be a late manifestation of virus infection which in higher titre causes death with lesions in the liver. The virus has been isolated from eight transplantable human tumours maintained in vivo: HEp 1, 3, 4, and 5, HS 1, HEmbRh 1, HAd 1, and A-42.[13–15] It has also been isolated from the liver and spleen of patients with cancer, but not from their tumours. The livers of rats bearing these transplantable tumours have also been found to contain the virus. Electron microscopy of infectious filtrates shows particles mainly of 70 mμ in diameter, many of which contain a nucleoid 18–25 mμ in diameter. Similar particles have been seen in the HEp 1 tumour. Cell-free filtrates obtained from four human tumours (HEp 1 and 2, HS 1, and HeLa) grown in vitro have not contained the agent. Also various transplantable mouse tumours (Crocker sarcoma 180, Ehrlich carcinoma, Bashford carcinoma, and glioma 26), three spontaneous mouse mammary tumours, the Jensen rat sarcoma, and the Walker rat carcinosarcoma failed to yield the agent. The virus has not been found—with one possible exception which is not fully described—in normal tissues from rats, mice, or hamsters.

Toolan et al. are careful to point out that there is at the moment no evidence that this new virus is a cause of the tumours from which it has been recovered. Indeed, they modestly end their paper: "While the significance of the agent in oncology is unknown, it is assumed that others will wish to know of these observations." It can be safely assumed that others will so wish and will endeavour to confirm these potentially important observations.

INTRAGASTRIC OXYGEN

NEWBORN babies commonly suffer from severe asphyxia, but most recover quickly and there is no call for treatment, apart from such simple measures as clearing the airway and keeping the child warm in the head-down position. But regular respiration is occasionally delayed for several minutes, and active resuscitation is then necessary. In the management of these cases intragastric oxygen has been used widely in this country following the original report of Akerren and Fürstenberg.[1] The evidence in favour of this procedure is slight and mostly clinical, and recent experimental work by Coxon[2] in Oxford and Cooper et al.[3] in Newcastle has thrown doubt on its value.

In a series of experiments on cats, kittens, and puppies Coxon measured oxygen saturation in arterial and portal blood before and after gastric insufflation with oxygen. The results were compared with those obtained in a group of anoxic cats which were either not treated or had insufflation of room air. Under the conditions of the experiment Coxon was unable to demonstrate any benefits from the intragastric administration of oxygen. His findings in regard to portal blood do not confirm the claim of Poupa et al.[4] that the introduction of oxygen into the small intestine of rats raises the oxygenation of the portal hæmoglobin by 25%.

Cooper et al., in their examination of the efficacy of intragastric oxygen, found that it made no difference to the survival-time of newborn kittens deprived of intrapulmonary oxygen. In the terminal stages, when cardiac arrest was imminent, they were unable to revive kittens by means of intragastric oxygen, but were successful when the lungs were ventilated with oxygen. The Newcastle workers conclude that the average newborn kitten requires 0·30 ml. oxygen per minute for bare cardiovascular survival, but that under the most favourable circumstances no more than 0·02 ml. per minute passes from the entire alimentary tract to the mesenteric blood. Much of this oxygen will be consumed in passage through the anoxic liver, for it is likely that the ductus venosus closes functionally within a few minutes after birth. The proportion of oxygen reaching the systemic circulation must be so small as to be insignificant.

These observations relate to animals, but there has been recent confirmation from two sources of the failure of intragastric oxygen to oxygenate arterial blood in the newborn infant [5, 6] There is no comparable evidence to support the claim that this is a useful procedure, and there is the further consideration that the use of intragastric oxygen carries certain risks and may delay the institution of more effective resuscitative measures [7] The therapeutic claims for intragastric oxygen have been seriously challenged, and the onus now lies upon those who recommend its use to produce quantitative evidence of its value

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[9] Montagu, A. The Natural Superiority of Women. London, 1954.
[10] *Lancet*, 1959, ii, 277.
[11] Toolan, H. W., Dalldorf, G., Barclay, M., Chandra, S., Moore, A. E. *Proc. nat. Acad. Sci., Wash.* 1960, 46, 1256.
[12] Toolan, H. W. *Science*, 1960, 131, 1446.
[13] Toolan, H. W. *Cancer Res.* 1954, 14, 660.
[14] Toolan, H. W. *ibid.* 1957, 17, 418.
[15] Skiff, J. V., Stein, A. A., Maisel, M., Heilbrunn, C., Hertz, D. *ibid.* 1958, 18, 485.

[1] Akerren, Y., Fürstenberg, N. *J. Obstet. Gynæc. Brit. Emp.* 1950, 57, 705.
[2] Coxon, R. V. *Lancet*, 1960, i, 1315.
[3] Cooper, E. A., Smith, H., Pask, E. A. *Anæsthesia*, 1960, 15, 211.
[4] Poupa, O., Kopecky, M., Chvel, F. *Nature, Lond.* 1957, 179, 1050.

MENTAL-HEALTH RESEARCH

THE dismal facts of mental illness have been repeated so often that they have lost some of their impact Sadly little response can now be generated by statements that nearly half the hospital beds in this country are filled by psychiatric patients, that something more than 1 person in 20 can expect to be admitted at some time to a psychiatric hospital, and that about a third of all absences from work are attributable to neurosis And relatively little research is directed at improving this situation the Medical Research Council, for example, put only 4¹/₂% of its total expenditure for 1959–60 into psychiatric work Too few trained workers and not enough immediately promising lines of approach are partly to blame, but lack of money and opportunity has always been crucial

To meet this need, a group of doctors, other scientists, and laymen started, in 1949, the Mental Health Research Fund, a charitable and independent body that collects money from wherever possible to establish research and travelling fellowships, to support specific lines of study, to organise conferences, and to award prizes Slow at first to gain momentum, the Fund gave the first grants in 1954—a humble £3129 in that year Growth has been steady and the annual report [8] for 1959–60 tells of £30,227 spent in research projects and of support for 25 new studies, ranging from the foster home to the effects of stress on monkeys The total so far spent exceeds £133,000, and a great many centres in this country are conducting research sponsored wholly or in part by the Fund The breadth of projects finding shelter beneath this wing is striking animal ecology, the training and follow-up of the mentally subnormal, the elucidation of new syndromes, mental-hospital sociology, the psychology of brain damage the long list shows perhaps special emphasis, however, on fundamental studies of biochemistry and neurophysiology For the first time the Fund's report can include a substantial list of papers published by award holders, 27 in all Support for short individual research projects, though taking most of the money, has been only one of the Fund's activities Thus, in 1952, it organised a conference at Oxford on prospects in psychiatric research, followed by contributions to four symposia on child development at Geneva and symposia on the nervous system at Oxford, Aarhus, and Strasbourg Seven books have emerged from these gatherings and an eighth, *Stress and Psychiatric Disorder,* just published, (see page 1124) arose from the Fund's 1958 conference [9]

Surveying the progress of the Fund so far, Mr Ian Henderson, chairman of the executive committee, told the annual general meeting on Oct 31 of a new departure—a £250,000 appeal to endow permanent research posts The Fund had become increasingly concerned with the research structure, particularly the lack of permanent prospects for those who devote themselves to this work A "vicious circle" led to first-class men going elsewhere, to fewer applications for research appointments, and consequently to fewer research vacancies being created Mr Henderson noted that three branches of the Government were involved the Minister of Health, the Minister of Science via the Medical Research Council, and the Chancellor of the Exchequer via the University Grants Committee, and therefore no one person was responsible for mental-health research as a whole Regular sums should be set aside for the missing chairs and readerships, and an increase in voluntary support, Mr Henderson believed, would force the State to take action

Emphasising the dearth of psychiatric research in British universities (where it should be done), Sir Geoffrey Vickers said that only 9 university psychiatric departments existed in this country and, of these, 6 had been set up since the war Difficulties in the early formative years, plus clinical and teaching demands, had made it very hard for these departments to conduct much research as yet, and the chair of experimental psychiatry at Birmingham University remained unfilled Government action in promoting work of this kind was sometimes impeded by the universities' legitimate demands for independence, but Sir Geoffrey explained that the Mental Health Research Fund, as a private benefactor, could achieve this more readily by offering help to those universities that seemed most receptive If we made an effort comparable to that in the physical sciences (including bringing in the most promising men), Prof J Z Young told the meeting he believed we should soon learn how to learn, how to discover, and how to avoid those breakdowns in the brain which constitute mental illness

A relatively small sum could transform the academic world of psychiatry, and it is no longer fanciful to hope that a breakthrough in biochemistry may release a hundred thousand people in this country from the grip of schizophrenia The Mental Health Research Fund deserves vigorous support in its efforts to accelerate progress

WHERE DO WE FIND MICROBES?

THE modern microbe hunter is not the pathologist trying to find the causal organism, but a teacher, student, or research-worker looking for microorganisms that are either typical and so suitable for teaching, or have particular properties such as the production of antibiotics, or depend on particular substances for growth To find out what organisms were kept in different laboratories, and to help in the interchange of cultures, an organisation with the cumbersome title of British Commonwealth Collections of Micro-organisms was set up in 1947 With the exception of South Africa, the larger countries of the Commonwealth formed national committees which collected information and issued directories in 1951 [1]

New editions of directories covering the United Kingdom,[2] Canada,[3] India,[4] Australia,[5] and New Zealand [6] have just been published These give the names and address of laboratories whose directors have indicated their willingness to distribute cultures to those who want them, and show what types of organism (algæ, protozoa, bacteria, fungi, yeasts, viruses) are kept in the different collections The directories with their lists of species do not form a *Who's Who* for microorganisms, and, since each directory has had a different set of editors, they provide many examples of the subjectiveness of taxonomy On nomenclature each director probably reflects the prevalent opinion of the country, but the directories should not be taken as a guide to correct usage

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[5] James, L S Moya F Burnard, E D , Apgar, V *Lancet*, 1959, i, 737
[6] Nelson N P *ibid* 1960 i 317
[7] Barrie H *ibid* 1959 i 684
[8] Mental Health Research Fund Annual Report 1959-60 39, Queen Anne Street London, W 1 Pp 28
[9] See *Lancet* 1958 ii 205

[1] See *Lancet* 1951 ii 1028
[2] Directory of Collections and List of Species Maintained in United Kingdom Ghana and Trinidad H M Stationery Office 12*s* 6*d*
[3] H M Stationery Office 9*s*
[4] H M Stationery Office 6*s*
[5] H M Stationery Office 8*s*
[6] H M Stationery Office 3*s*

The lists of species were made up from replies to questionaries sent out (in the U K at least) in 1958, and in a recent test it was found that several laboratories have lost or discarded some of the strains listed in that year Furthermore, the published lists do not contain strains added since With the reservation that the lists are not as up to date as they might be, they will still be useful to those seeking cultures So far these lists of Commonwealth collections are the most comprehensive available It is cheering news that plans are being made to extend the work to other countries so that a world-wide directory can be prepared

AMBULANCES

WE have always wondered who designs our ambulances We accept them as we accept instrument bowls and bedpans they are not perfect but we do not know of better Bothwell [1] has now put forward some ideas for improving the ambulance No-one, least of all the patients, would deny the virtues which he claims for his design Independent springing would make for smooth riding, and front-wheel drive for a low floor easy of access for walking patient or stretcher Indeed Bothwell would go further than this he suggests a mechanism by which the body of the ambulance could rest on the ground while it is being loaded

Perhaps the most important lesson of this article is the small part that our profession plays in what is basically a medical (or surgical) problem Under the Act of 1948 the ambulance services are the responsibility of the local authorities Though nominally under the control of the medical officer of health, in many counties and county boroughs they are organised and managed by a staff which is entirely lay We believe that every ambulance carries at least one man trained in first-aid, but the experience of some practitioners suggests that those who control the service do not always appreciate the finer points about moving sick people Yet few M O H s can afford to appoint a medical member of their staff as a full-time ambulance officer A reasonable solution is not easy to find, but no-one must forget that in cases of doubt the medical opinion ought to override all other considerations

If our ambulances carried emergency cases only (as they do in many parts of the U S A) the organisation of the service would not be so difficult As it is, most ambulances spend at least as much time in ferrying those who cannot use public transport to the outpatient departments In rural districts the result is a milk round which may take up to four hours—and four hours in the best ambulance in the world is no joke if you have an ununited fracture Wireless control of the ambulances from the control room is almost universal, and beyond doubt this makes for economy, but it is not good for the morale of a patient that while he is going to hospital the ambulance is diverted twenty miles to pick up some other unfortunate Helicopters are expensive to buy and to run (and infernally noisy), but their use might do much for the comfort of patients Those who have had the opportunity of seeing the type of helicopter used, and the way they were used, after the disaster at Frejus might bring the matter to the notice of the Minister of Health

During the late war a distinguished D D M S described the ambulance as among the most lethal weapons of war yet invented It was certainly true on most fronts that the longer the carry the worse the prognosis This was not only because treatment was delayed but also because in a moving ambulance the wounded man never had a moment's rest, however careful the driver and kind the attendant In contrast, evacuation by air was peaceful and almost soporific Our ambulances today are far grander than those used by the Army and our roads are smoother, but a journey by ambulance can be a very real ordeal for the seriously injured Some patients stand travel better than others, but it is generally true that the faster the ride the more uncomfortable it is There is a romantic idea still abroad that the ambulance, like the fire engine, should be subject to no traffic regulations In this country ambulances enjoy no statutory privileges (since such privileges were withdrawn from the New York City ambulances the number involved in accidents has fallen by half [2]) On a journey of 10 miles the difference in time between average speeds of 20 m p h and 40 m p h is 15 minutes It can be very seldom that this time, taken in conjunction with the times for loading and unloading, makes any difference to a patient's chances of survival Far more often, if the vehicle travels slower the relative absence of vibration and more violent movements will be to the patient's benefit. In a study in Michigan of 2500 consecutive ambulance runs it was found that in 98 2% haste was needless and that a saving of 5 minutes would not have influenced the course of a single injury [3] It would be interesting to see comparable figures from one of our own hospitals The elderly practitioner who told the ambulance to come like Jehu and return like Agag gave very sound advice

ISOENZYMES

DETECTION of increased plasma and serum enzyme activities has proved useful in the diagnosis of myocardial disease [4,5] The changes are not specific, for they may be found also in diseases of the liver, the biliary and pancreatic tracts, and skeletal muscle Confusion may also arise from the administration of drugs, such as the promazines, certain anticoagulants, and opiates, which may also lead to increased serum enzyme activity

Various enzymes, it now seems, may turn out to be mixtures of several different components, called isoenzymes, which closely resemble each other in their biological activity but differ serologically and chemically, as well as in their behaviour during electrophoresis [6,7] In different tissues, the pattern of distribution of the isoenzymes varies, and it should, therefore, be possible to recognise disease of a tissue by virtue of the fact that its isoenzyme pattern becomes duplicated in the plasma This, of course, applies only to those diseases which result in release of tissue-enzyme content

Particular attention has been applied by Wroblewski

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et al[8] to lactic acid dehydrogenase, which they have investigated by the technique of starch-gel electrophoresis[9] This is carried out in a rectangular starch-gel, and the enzyme activity for every 0 3 cm of the gel length can be determined by cutting out segments of appropriate size, peaks of activity can then be demonstrated at different positions along the gel Tissue lactic acid dehydrogenase has thus been shown to consist of at least five components, referred to as LD_1, LD_2, LD_3, LD_4, and LD_5[6] The higher the number of the component, the greater its mobility during electrophoresis In normal human plasma, the LD_4 activity is slightly greater than that of LD_5, and these two are the major components, there are apparently sometimes four[6] and sometimes five[8] isoenzymes Extracts of heart muscle contain the same two major components, but LD_5 predominates over LD_4 In liver tissue LD_1 predominates In skeletal muscle, too, LD_1 predominates, but an appreciable amount of the other isoenzymes is present Spleen shows a preponderance of LD_2 and, to a lesser extent, of LD_4 Kidney shows a preponderance of LD_5, LD_4, and LD_3, in that order Characteristic patterns are also obtained with human pancreas and human lung, in fact, each tissue so far examined seems to have a special distribution of these isoenzymes

In the diagnosis of myocardial infarction some of the limitations of plasma-enzyme estimation should be overcome by measuring the plasma-isoenzyme pattern of lactic dehydrogenase activity Diseases of the liver, skeletal muscle, biliary tracts, lung, and other organs cause changes in the pattern which are characteristic of the organ or the pathological process, or both, but are not similar to those found with myocardial infarction The plasma-isoenzyme pattern characteristically associated with myocardial infarction should reflect myocardial necrosis more distinctly than the plasma-enzyme tests previously used The abnormal pattern can be recognised even though the plasma-enzymes are within normal limits, and it persists appreciably longer than does, for example, the rise in serum-transaminase

Isoenzymes, besides those of lactic acid dehydrogenase, are being investigated in several laboratories, and this exciting new development points very strongly to the possibility of a kind of " finger-print " diagnosis by examination of a patient's serum In this way, in the not too distant future, it may be possible to demarcate, with some certainty, disease of an organ or organs

SPECIFIC MESENTERIC LYMPHADENITIS

" MESENTERIC adenitis " is an all-too-handy diagnostic rag-bag for ill-defined and evanescent disorders As with most obscure infections, a viral origin has been suggested, but no virus has been identified Aird[10] noted that 37 cases were admitted to a children's hospital in a period when admissions for appendicitis numbered 83 The disease is therefore quite common, and if it could be diagnosed without laparotomy many patients could be spared operation Taylor[11] has lately reported 49 cases

Continental workers showed that mesenteric adenitis may arise from infection with *Pasteurella pseudotuberculosis* Knapp[12] reported 117 such cases observed in 1954–57 Most were diagnosed on serological evidence, but the causal organism was isolated from the lymph-nodes in 13 cases and from blood in 2 others The first report from this country seems to be that of Mair et al,[13] who, in a thorough investigation of 17 cases of mesenteric lymphadenitis, found evidence of pasteurella infection in 3 The material examined consisted of appendix, fæces, throat-swab, serum, and, in all but 5 cases, excised mesenteric lymph-nodes The nodes and appendices were examined bacteriologically and histologically, the sera were titrated for antibodies to *Past pseudotuberculosis*, and the fæces, throat-swabs, and nodes were cultured for viruses on amnion and monkey-kidney cells No virus was isolated, but antibodies to *Past pseudotuberculosis* were found in 3 cases, and in 2 of these the organisms were cultured from the lymph-nodes

Past pseudotuberculosis is a short gram-negative bacillus closely related to the plague bacillus and is most often found as a parasite of small rodents—particularly guinea-pigs and rats—but it has been recorded occasionally in domestic animals and birds The specific name derives from the appearance of the lesions caused, which macroscopically resemble those of tuberculosis Little is known of the natural spread of the disease, but animals may be infected experimentally by feeding, and the site of the lesions suggests infection by the intestine Infections in man are especially common in winter, perhaps because of an adverse effect by cold on the animals which provide the reservoir

The 3 British cases were subacute infections diagnosed clinically as appendicitis, although in 1 the possibility of mesenteric adenitis was considered Agglutinins, present to titres of 1 in 300, 500, and 3000, would have suggested the diagnosis in each case had the sera been tested before operation, but the detection of antibodies during an attack is only presumptive evidence of ætiology, and the surgeon may still consider laparotomy advisable

Mair et al recommend culturing at 22°C as well as at 37°C One of their isolations would not have been made without this precaution Misleading serological reactions seem to be rare, Knapp found none in children with typical appendicitis or in over 1000 sera collected for Wassermann reactions Two uncommon types of *Past pseudotuberculosis* share antigens with salmonellæ, and it is therefore occasionally necessary to carry out agglutinin-absorption tests to verify the serological diagnosis In uncomplicated cases antibodies do not persist for more than a few months Gross and microscopical appearances of the mesenteric nodes may suggest the diagnosis, but these appearances do not have the certainty of bacteriological evidence

Pseudotuberculosis due to pasteurellæ is found chiefly in those aged 2–5 and 12–23 years, boys are much more commonly affected than girls Occasionally the disease assumes a septic form with typhoidal symptoms and a high mortality In mild cases no specific treatment is needed, though, even in such cases, it may be advisable to use chemotherapy when serum-antibodies persist at a high level Experiments by Knapp suggested that streptomycin or the tetracyclines were the antibiotics of choice The British strains were sensitive in vitro to these drugs and also to chloramphenicol, polymyxin, neomycin, and nitrofurantoin, but were resistant to penicillin, erythromycin, oleandomycin, novobiocin, bacitracin, and sulphafurazole

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Special Articles

STERILISATION OF RADIUM NEEDLES AND GYNÆCOLOGICAL APPLICATORS

R J FALLON
B Sc , M D Lpool
LECTURER, UNIVERSITY DEPARTMENT OF BACTERIOLOGY,
WESTERN INFIRMARY, GLASGOW, W 1

STERILISATION procedures have recently undergone careful scrutiny and in many instances deficiencies in present methods have been demonstrated (Howie and Timbury 1956, Nuffield Provincial Hospitals Trust 1958) Boiling does not guarantee sterility and is open to abuses (Nuffield Provincial Hospitals Trust 1958), and Perkins (1956) has suggested that it should not be used as a sterilisation process if more reliable methods such as pressure-steam sterilisation are available

At present radium needles and gynæcological applicators are boiled before use, and to replace this method by the use of a conventional pressure-steam steriliser would raise difficulties, because the lead necessary to provide complete protection from the gamma-radiation of the radium that might be used for only one patient would weigh 100 lb or more

The Investigation

It was decided, therefore, to investigate the possibility of sterilising radium needles and gynæcological radium applicators in a domestic pressure-cooker (fig 1) This container has the advantage that it is so small that the major part of the protective lead screen can be placed around it, and only the small lead block in which the radium needles are to be carried to the radiotherapist need be placed inside

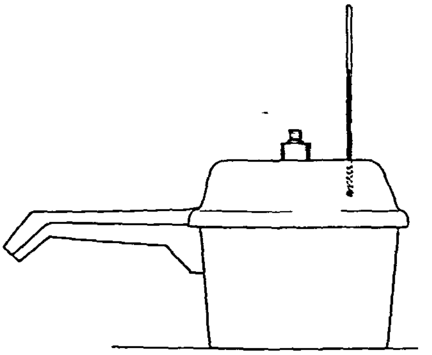

Fig 1—Pressure-cooker used in this investigation A thermometer was inserted through the safety plug

MATERIALS AND METHODS

Radium containers—Dummy radium needles were made from stainless-steel rods They were longer than real needles to facilitate their removal from the lead blocks under test, and they were also of greater diameter (3 mm as compared with a maximum diameter of 1 95 mm for radium needles) Dummy inserts for ovoids were also made of stainless steel Before being used in experiments the rods were coated with spores of *Bacillus stearothermophilus*

The spores—These were prepared by a modification of the method described by Alder and Gillespie (1957) The spores used in the majority of experiments, when tested on filter-paper strips, survived 4 but not 10 minutes' exposure to steam at 121°C (15 lb per square inch) After being exposed to steam, test-spore papers were cultured in 1% glucose-peptone water at 60°C Dummy radium needles were similarly cultured after they had been heated in the various experiments Unheated positive controls were included in all experiments whether with spore-papers or dummy radium needles Tests were read when these positive controls showed growth with the production of acid This usually happened after overnight incubation Incubation of heated spores for periods of up to 18 days beyond the time when the positive controls showed growth did not increase the number of positive cultures obtained

EXPERIMENTAL STUDIES

Radium Needles

Preliminary experiments showed that it was not possible to sterilise dummy radium needles in a pressure-cooker if they were placed in the lead block normally used for holding them during boiling This block had blind-ended holes for holding the needles and as air removal in a pressure-cooker depends upon turbulence it is probable that failure to sterilise was due to air being trapped in the small space between the needles and the sides of the holes in the block

To overcome this difficulty a modified rectangular lead block was designed (fig 2) Holes 5 mm in diameter were drilled right through the block 2 mm below the block a metal plate was attached on which the needles rested This design of block had the advantage that the active part of the radium needle (which occupies the central part of the needle to within 5 mm of each end) was still screened laterally but steam could circulate freely through the holes The base plate was not perforated

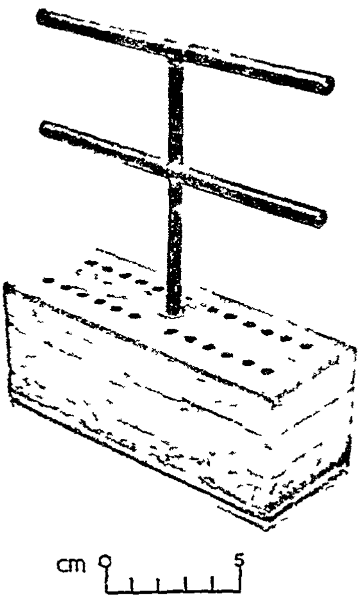

Fig 2—Modified rectangular lead block with holes drilled right through the block and a metal plate below the block to support the needles

Experiments were conducted to find out (1) whether the needles could be sterilised in the block, (2) whether the block impeded sterilisation as judged by comparing the sterilisation of needles outside and needles inside the block, and (3) whether needles heavily contaminated with blood could be sterilised in the block

Results

Sterilisation of spore-coated needles—The results of experiments with the modified block are shown in table I In these experiments the dummy needles were heated for two different times at 121°C, the block being placed upright in the pressure-cooker Heating for 10 minutes sterilised most of the needles, and heating for 15 minutes sterilised all of them Spores of the same batch, tested on filter-paper strips, were killed by being steamed at 121°C for 10 minutes but not for 4 minutes

Experiments comparing the sterilisation of needles inside the block with those lying free—In these experiments the dummy radium needles were coated either with spores or a mixture of horse-blood and spores The needles outside the block lay on a sheet of wire gauze above the level of the water in order to avoid any possible washing-off of the spores by the boiling

TABLE I—STERILISATION BY STEAM AT 121°C OF DUMMY RADIUM NEEDLES COATED WITH SPORES OF *B stearothermophilus*

Minutes at 121°C	No of needles showing survival of spores	Total needles in test
10	3	17
15	0	30
0 (unheated controls)	33	33

water The results of experiments where the needles were heated at 121°C for 10 minutes are shown in table II

This particular time of exposure to steam at 121°C was chosen because it was known that only a proportion of the needles would be sterilised and thus any impairment of sterilisation by the block would be obvious It is apparent that the block did not interfere with sterilisation of the needles

Effect of the presence of blood on the sterilisation of radium needles—In the absence of full remote-handling facilities, washing radium needles presents a hazard to the radium handler and needles may not always be cleaned thoroughly To assess the effect of blood-contamination on the sterilisation of needles a mixture of one part of horse-blood to three parts *B stearothermophilus* spore suspension was made Needles were coated with this mixture, then dried The effect of blood on the sterilisation of these needles is clearly shown in table II Whereas approximately five out of every six clean needles were sterilised after 10 minutes at 121°C, only half of the blood-coated needles were sterilised All of 30 blood-coated needles were sterilised after exposure to steam at 121°C for 15 minutes whether they lay inside or outside the block

TABLE II—EFFECT OF LEAD BLOCK UPON STERILISATION OF DUMMY RADIUM NEEDLES BY EXPOSURE TO STEAM AT 121°C FOR 10 MINUTES

Needles coated with	Needles inside block	Needles outside block	Unheated controls
B stearothermophilus spores only	7/41 (*17%*)	4/25 (*16%*)	20/20
B stearothermophilus spores and horse blood	13/25 (*52%*)	8/15 (*54%*)	10/10

Numerator needles showing survival of *B stearothermophilus* spores
Denominator – total number of needles in test

These experiments show that dummy radium needles when coated with heat-resistant spores and blood can be sterilised in a block of the general design illustrated in fig 2 The block used for these experiments does not, however, provide the maximum desirable protection against radiation for the person who has to carry it from the lead-screened pressure-cooker to the user

With the aid of Mr T McAinsh, B SC, of the Western Regional Physics Department, an improved block was designed This cylindrical lead block (fig 3) is 10 cm in diameter and 6 cm deep and weighs approximately 5 5 kg (12 lb) It will hold 24 needles in holes 5 mm in diameter When fully loaded, the radiation level at the centre of the block surface is 3 röntgens per hour and at 15 cm from the block is 1 röntgen per hour Because this block will be handled with long tongs and for very short periods only, it provides a good margin of safety

As there is considerably more lead in this block than in the modified block used for most of the experimental work, a perforated base plate was introduced to ensure good steam circulation through, and air removal from, the block It seemed possible that the increased mass of lead would take so much heating that the temperature within the block might lag behind that in the rest of the pressure-cooker thus interfering with the sterilisation of needles within the block Thermocouples placed both in the holes in the block and also in a blind-ended hole in the block have failed to show any such temperature lag

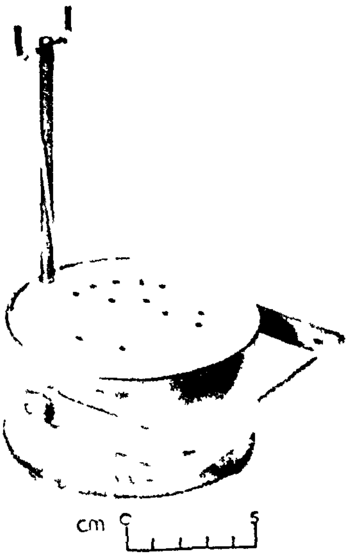

Fig 3—Cylindrical metal block This has a carrying handle and a brass arm to which are attached the silk threads from the radium needles

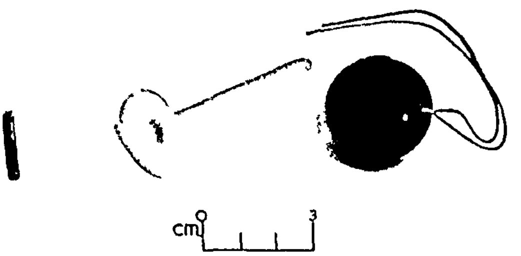

Fig 4—Radium container, rubber cavity tube, and ovoid

Experiments comparing the sterilisation of needles outside and inside the block have shown that 10 of 55 (18%) needles inside the block showed spore survival after exposure to steam at 121°C for 12 minutes as compared with 10 of 48 (21%) needles outside the block These results suggest that the block does not interfere with sterilisation (12 minutes' exposure was used here as these spores were more heat-resistant than those used for the experiments shown in table II)

Gynæcological Applicators

The other radium sources considered in this study were those used in gynæcological work for the irradiation of the cervix uteri These are of two kinds (1) those contained in a rubber ovoid for irradiation of the vaginal vault, and (2) those contained in a rubber intrauterine tube (fig 4) Normally both these types of applicator are boiled before use

TABLE III—STERILISATION BY STEAM AT 121°C OF GYNÆCOLOGICAL RADIUM APPLICATORS CONTAMINATED WITH *B stearothermophilus* SPORES

Container	Minutes at 121 C	Number showing spore survival/ total tested
Ovoid	15	1/6
Uterine cavity tube	15	1/14 (2/14)*

* Showing growth after opening tube and culturing metal insert

The cavity tubes were made up as illustrated in fig 5, the metal insert being coated with spores of *B stearothermophilus* After being heated in the pressure-cooker, cavity tubes were cultured intact for 24 hours, then the metal inserts were removed and the tube and insert were cultured together for another 24 hours Unheated controls included in each test revealed that some batches of cavity tubes contained a substance or substances which inhibited the growth of *B stearothermophilus* It was found that repeated boiling of the tubes removed this inhibitor All tubes from "toxic" batches used in these experiments were tested, therefore, for an inhibitory effect both by incubating them in peptone water inoculated with *B stearothermophilus* and by boiling them with the spore-coated metal insert inside and then culturing the metal insert to see if any "toxic" effect was evident only on heating Despite the lack of toxicity eventually shown by these tests on tubes which had been repeatedly boiled, the inserts were latterly incubated alone

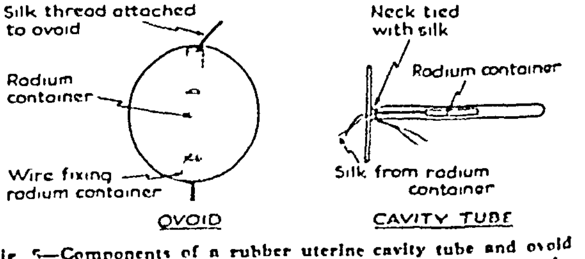
Silk thread attached to ovoid
Radium container
Wire fixing radium container
OVOID
Neck tied with silk
Radium container
Silk from radium container
CAVITY TUBE

Fig 5—Components of a rubber uterine cavity tube and ovoid Only one radium container is shown in the uterine-cavity tube Normally this tube would be filled with two or three containers

TABLE IV—EFFECT OF VARYING CONDITIONS UPON THE STERILISATION OF GYNÆCOLOGICAL APPLICATORS BY EXPOSURE TO STEAM AT 121°C FOR 15 MINUTES

Container	Conditions	Number of containers showing spore survival/total tested
Ovoid	Placed above water	5/11
	Immersed	1/12
Uterine cavity tube	Packed with dry metal insert	0/22 (unheated controls +ve)
	Packed with moistened insert	0/22 (unheated controls +ve)

Ovoids and their inserts were coated with spores of *B. stearothermophilus* or with a mixture of spores and blood and were then dried. After heating, ovoids and inserts were cultured in 1% glucose-peptone water at 60°C. No evidence of a "toxic" effect was noted in experiments with ovoids.

Results

When cavity tubes and ovoids were heated above the level of water in the pressure-cooker not all of them were sterilised by exposure to steam at 121°C for 15 minutes (table IV). This may well have been due to air pocketing in and consequent failure of steam penetration into both the cavity tubes and the central cavity of the ovoid. Experiments were, therefore, carried out with the cavity tubes to see whether moistening the insert before placing it in the cavity tube would help to overcome this difficulty. As may be seen from table IV the results were equivocal.

Air pocketing in ovoids can be overcome by immersing them in the water in the pressure-cooker. Table IV shows the results of experiments comparing the proportion of ovoids sterilised when heated above the water in the pressure-cooker with the proportion sterilised when the ovoids were immersed in water. It may be seen that immersing them during sterilisation increased the proportion of ovoids sterilised by heating for 15 min. at 121°C.

One ovoid immersed was not sterilised after 15 minutes at 121°C. This is not surprising in view of the difficulty of sterilising the tracks through which the wire securing the radium container to the ovoid passes and those through which the silk thread passes.

In subsequent tests with metal inserts coated either with blood and spores, or with spores alone, all of 68 ovoids failed to show spore-survival after heating for 20 min. at 121°C in the water in the pressure-cooker. This result was due to sterilisation and not simply to a dilution effect, because ovoids boiled in the water in the cooker for 20 minutes showed growth of *B. stearothermophilus* on culture.

Discussion

These experiments show that it is possible to sterilise dummy radium needles within a pressure-cooker. As real radium needles are thinner than the dummy needles they will allow easier access of steam into the holes in the block with presumably still greater efficiency of sterilisation. The block described is the largest size that would be needed for one patient. Smaller blocks of a similar design could be used for smaller numbers of needles. It is surprising that inserts in uterine-cavity tubes can be sterilised, because in these tubes conditions for steam sterilisation would seem to be poor. Ovoids required heating for 20 minutes at 121°C to ensure their sterility, perhaps because of the various tracks through the rubber where steam penetration may be difficult. Since the spores used in these experiments were more heat-resistant than those of pathogenic bacteria, an additional safety margin is introduced.

To ensure that sterilisation is accomplished, a few simple precautions should be taken. The eyes of needles and other radium containers should be kept clean, perhaps by treatment in an ultrasonic instrument-washer to avoid handling problems, so that bacteria are not buried in a protein coagulum and protected from access of steam. Ovoids should be immersed in water in the pressure cooker and radium containers should be moistened before being placed in uterine-cavity tubes. It is essential in order to remove all the air, that steam be allowed to flow freely from the pressure cooker for at least 2 minutes after the water boils, and before placing the weights on the steam outlet. If this is not done the correct temperature will not be reached inside the cooker. All articles should be steamed for 20 minutes at 121°C (i.e., 15 lb per sq. in.). Care must be taken to ensure that the cooker does not boil dry in view of the possibility of damage to the radium containers.

By using these methods the provision of sterile radium needles and gynæcological applicators becomes a simple but sure procedure without raising major handling problems. The radium sources are placed in the pressure-cooker (which could, if necessary, be carried from hospital to hospital) on an electric hotplate which lies behind a screen of lead bricks in a room next to the operating-theatre. Ideally there should be a communicating hatch between the operating theatre and the room in which the radium is to be sterilised so that the complete pressure-cooker, after being returned to atmospheric pressure, may be pushed into the theatre on to a lead-screened table. If this is not possible the pressure-cooker could be transferred to a trolley (suitably screened with lead) and thus brought into theatre.

Once in the operating-theatre the cooker can be opened when its contents are needed and the lead block (for radium needles) or the gynæcological radium may be carried with long tongs to the radiotherapist.

Summary

A simple method of sterilising radium needles and gynæcological applicators in a domestic pressure-cooker is described. Details are given of a modified lead block which ensures adequate circulation of steam round the needles. The necessary equipment is inexpensive and the amount of protective screening is reduced to a minimum.

I am grateful to Dr. A. A. Charteris, Director of Radiotherapy and National Radium Centre, Western Infirmary, and to Dr. Mary A. C. Cowall of that department for many helpful discussions. The prototype lead block was made by Mr. A. MacDonald. The final model was made by the Western Regional Physics Laboratory. The photographs are by Mr. G. R. Kerr and the drawings by Mr. R. Callender.

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"In 1958 world population was 2852 million, the annual rate of increase is 1·7 per cent, far higher than it has ever been before. Unless birth-rates are reduced, many nations of Asia will be unable to achieve an economic break-through from a state of underdevelopment and underemployment to a developed and developing economy. This is because the demand for servicing the additional population will make it impossible to provide adequate finance for industrialisation and technological development. Whatever can be done about food production, in Africa for instance, can only help for a very few years, if the present rate of population increase continues. Even if you could keep food production sufficiently high to feed the net yearly increase in population (which is doubtful), it is impossible at the same time to catch up with the lag of undernourished human beings, who constitute two-thirds of the people of the world."—SIR RUSSELL BRAIN, DR. JULIAN HUXLEY, *Times*, Nov. 10, 1960, p. 13.

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Numerator = needles showing survival of *B stearothermophilus* spores
Denominator = total number of needles in test

These experiments show that dummy radium needles when coated with heat-resistant spores and blood can be sterilised in a block of the general design illustrated in fig 2 The block used for these experiments does not, however, provide the maximum desirable protection against radiation for the person who has to carry it from the lead-screened pressure-cooker to the user

With the aid of Mr T McAinsh, B SC, of the Western Regional Physics Department, an improved block was designed This cylindrical lead block (fig 3) is 10 cm in diameter and 6 cm deep and weighs approximately 5 5 kg (12 lb) It will hold 24 needles in holes 5 mm in diameter When fully loaded, the radiation level at the centre of the block surface is 3 rontgens per hour and at 15 cm from the block is 1 rontgen per hour Because this block will be handled with long tongs and for very short periods only, it provides a good margin of safety

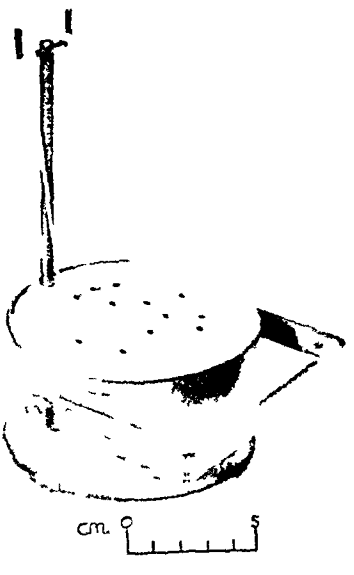

Fig 3—Cylindrical metal block. This has a carrying handle and a brass arm to which are attached the silk threads from the radium needles

As there is considerably more lead in this block than in the modified block used for most of the experimental work, a perforated base plate was introduced to ensure good steam circulation through, and air removal from, the block It seemed possible that the increased mass of lead would take so much heating that the temperature within the block might lag behind that in the rest of the pressure-cooker thus interfering with the sterilisation of needles within the block Thermocouples placed both in the holes in the block and also in a blind-ended hole in the block have failed to show any such temperature lag

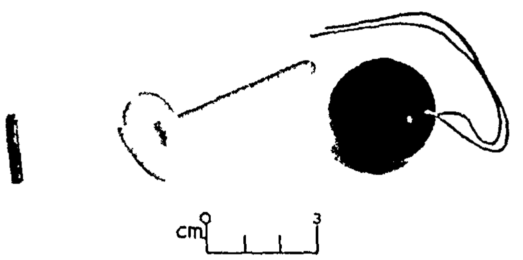

Fig 4—Radium container, rubber cavity tube, and ovoid

Experiments comparing the sterilisation of needles outside and inside the block have shown that 10 of 55 (18%) needles inside the block showed spore survival after exposure to steam at 121°C for 12 minutes as compared with 10 of 48 (21%) needles outside the block These results suggest that the block does not interfere with sterilisation (12 minutes' exposure was used here as these spores were more heat-resistant than those used for the experiments shown in table II)

Gynæcological Applicators

The other radium sources considered in this study were those used in gynæcological work for the irradiation of the cervix uteri These are of two kinds (1) those contained in a rubber ovoid for irradiation of the vaginal vault, and (2) those contained in a rubber intrauterine tube (fig 4) Normally both these types of applicator are boiled before use

TABLE III—STERILISATION BY STEAM AT 121°C OF GYNÆCOLOGICAL RADIUM APPLICATORS CONTAMINATED WITH *B stearothermophilus* SPORES

Container	Minutes at 121 C	Number showing spore survival/ total tested
Ovoid	15	1/6
Uterine cavity tube	15	*1/14 (2/14)**

* Showing growth after opening tube and culturing metal insert

The cavity tubes were made up as illustrated in fig 5, the metal insert being coated with spores of *B stearothermophilus* After being heated in the pressure-cooker, cavity tubes were cultured intact for 24 hours, then the metal inserts were removed and the tube and insert were cultured together for another 24 hours Unheated controls included in each test revealed that some batches of cavity tubes contained a substance or substances which inhibited the growth of *B stearothermophilus* It was found that repeated boiling of the tubes removed this inhibitor All tubes from " toxic " batches used in these experiments were tested, therefore, for an inhibitory effect both by incubating them in peptone water inoculated with *B stearothermophilus* and by boiling them with the spore-coated metal insert inside and then culturing the metal insert to see if any " toxic " effect was evident only on heating Despite the lack of toxicity eventually shown by these tests on tubes which had been repeatedly boiled, the inserts were latterly incubated alone

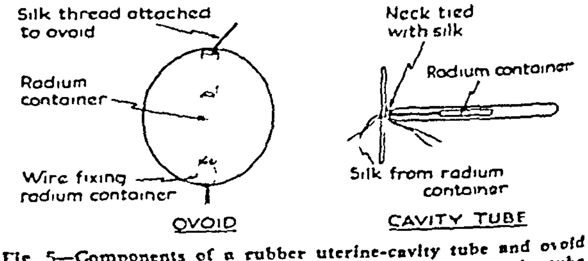
Silk thread attached to ovoid
Radium container
Wire fixing radium container
OVOID
Neck tied with silk
Radium container
Silk from radium container
CAVITY TUBE

Fig 5—Components of a rubber uterine-cavity tube and ovoid Only one radium container is shown in the uterine-cavity tube Normally this tube would be filled with two or three containers

In England Now

A Running Commentary by Peripatetic Correspondents

It is possible to render a cat neurotic in the following way First of all you teach it that food may be found under a certain lid Then you teach it to step on a lever A to put the food there Then you teach it that stepping on lever A only has this effect after a buzzer has sounded Then you teach it to step on another lever B which causes the buzzer to sound At this point the hungry cat, when put into the cage, goes to lever B, starts the buzzer, treads on lever A, sees the food travel along a moving belt to the box, and finally lifts the lid and takes the food The mental state of the animal at this stage of its training might fairly be compared with that of a membership candidate, his brain the precarious repository of an elaborate, arbitrary structure of yeas and nays, do's and don'ts, almost amounting to the behavioural equivalent of a Calder mobile

To return to the cat, it is instructive to watch the zest with which the experimenter next rigs up a cylinder of compressed air in such a way that, as often as not, but in no predictable sequence, the cat receives a violent air-blast in the face as it reaches triumphantly down into the box After several of these rebuffs, the wretched animal grows disgusted with a world in which it receives only a silent Bronx cheer at the very moment when it expects, if anything, a spot of applause, it becomes apathetic, uncertain, withdrawn It flinches at the sight of a mouse and has no heart for small talk with the fellers when it returns to the sane and levelheaded world of cats It is, as you might say, a cool and far-out catnik Several times a year one can see a silent, tight-lipped cortege of humans leaving Queen Square in this condition

And now, the moral The cat knows when it is beaten, whereas before it unerringly selected milk, now it totters on shaking paws to the dish of alcohol But what of its human counterparts? These do not, let it be said, all take to drink, but with the regularity and persistence of the very seasons they return, time after time, to go through the same ritual and receive sooner or later the ineluctable blasting This may not altogether go to show, as Clovis once put it, the superior wisdom of the cat tribe, but it makes you think, all the same

* * *

It looks as though the West Country has lost its floods for the time being at any rate, though when the snow comes to the moors what will happen to the valleys is anyone's guess But sufficient unto the day—down here we are busy scrubbing up for Christmas The ground-floor rooms in those thousand flooded houses look much alike Bare boards (for who would risk new lino or treasured carpet on still damp floors—a few rugs have to suffice), paper peeling from dripping walls, doors that will not shut, coldness and dampness everywhere But the furniture, what there is left of it, is polished to perfection and the brass door-step is brighter than ever, and above all there are countless fires

What of the inhabitants? There are some bruised shins and sprained ankles, the result of stepping into holes in the boards, a few colds, and fewer grumbles What really does hurt is when other towns claim to have had bigger and better floods than ours It just isn't fair! Anyhow we were one of the first on the news Our houses were on the telly and we could even recognise our friends on the screen We may salute Christmas with bare boards, bare walls, bare cupboards even, but salute it we will, and if the floods come again we will know how to deal with them and won't lose our carpets and lino the second time

* * *

It had been a long unsatisfactory case, with an inevitable conclusion The old man, on steroids for his chest, had failed to respond to medical treatment for his bleeding gastric ulcer Postoperatively his abdomen had dehisced twice, and he had had a deep-vein thrombosis His electrolytes had gone haywire, his serum-proteins had dropped, and he had become a pool of œdema Then, finally, he had begun to bleed again

The necropsy plodded on, nobody really learning very much The physicians looked for a surgical "cause of death", the surgeons were quite sure none of it would have happened if So when the pathologist pulled a calcareous 5 cm ×2 5 cm solitaire out of the gallbladder and placed it with a bang on the table, everybody applauded the anæsthetist's soft comment "Well, there is something concrete, anyway"

* * *

In my first house-job at the Z Royal Infirmary, I became convinced that the inhabitants of Z-shire had a bowel fixation Whatever their complaint, from congestive cardiac failure to disseminated sclerosis, the patient's chief anxiety was centred on the presence or absence of constipation Other symptoms and states might be unpleasant or inconvenient, only bowels were dangerous The Medical Registrar, who had worked among the Zians much longer than I had, maintained that if you asked a Zian how his chest was, he would say "all right", if you asked him how his stomach was, he would say "all right", but if you asked him how his bowels were, he would say "all right, thank you"

* * *

It was a mild sunny Sunday morning, and the bustling animated crowd at Sandown Park might have been out for a carefree day at the races But there were an unusual number of spectators in uniform—nurses, Civil Defence, ambulance, Red Cross, scouts, guides, and police There were signs of strange mishaps, too, in the incongruously cheery casualties who strolled around, swathed in gory bandages, their faces ashen-grey with makeup and powder In fact it was the Casualties' Union annual competition

I had rashly offered to lend a hand supervising the National Blood Transfusion Service demonstration My team was so expert that my own colour soon improved A rubicund "donor" and a pallid "casualty" were laid out side by side on stretchers "Blood" from drip-feed bottles ran to cannulæ in the antecubital fossa, artfully camouflaged with flesh-coloured plasticine The inflow to the donor and the outflow from the casualty were concealed beneath the blankets However, we all actually drank copious draughts of hot sweet tea, whenever the clot of spectators thinned

The main event was the competition in which 24 ambulance teams from Service, police, Civil Defence, London Transport, and first-aid organisations had to diagnose three set casualties, render emergency first-aid, and get them into the ambulance within ten minutes The "casualties" were strewn on the steps of the grandstand, acting the role of cleaners who had sustained injury while clearing up after the race-goers It was interesting to watch how the teams went about it I particularly relish the memory of a sweating policeman solemnly warning a casualty with a fractured tibia, "Now, you just stay where you are!"

* * *

The essential foreignness of a foreign country is never so strongly felt as in its hotels—the weird noises at odd hours, the cigar smells, the mysterious slept-in beds which appear overnight in the corridor, the pocket-filling keys attached to great bronze shields But the things that really make me feel homesick and ill at ease are the notices Sometimes this is because I cannot read them at all "XPTHNTH TNY KRPTHNTHCXH!" declared an authoritative-looking plaque in an Athenian lavatory (Zeus! I remember wondering for a sickening moment—was I sitting in the right half of that bicameral establishment?) But usually it is their sheer threateningness that disconcerts me "1 THE DIRECTION DON'T ANSWER FOR VALUES AND PRECIOUX THINGS, LEAVED UNGARDED IN THE ROOMS," growled a huge board in my Rome hotel Aghast, I carefully locked my pitiful possessions in the wardrobe and pocketed another 4 in key before going down to dinner Next day, when the key jammed in the door, I struggled with it in a state of mad, unreasoning panic, fearful lest I be delayed and get involved in some terrible, foreign legal proceedings For the next notice ran "2 ROOMS DON T DISAFFIRMED WITHIN 14 O'CLOCK ARE CONSIDERED CONFIRMED FOR THE NEXT DAY"

Letters to the Editor

REPRESENTATION OF REGIONAL BOARD HOSPITAL CONSULTANTS

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The National Health Service Act was negotiated without direct consultations with the consultants and specialists of non-teaching hospitals as a body, and now we have the "package deal" with its threat to part-time service The abolition of "weighting" for new consultant appointments and of travel allowances will cost some consultants about £700 per annum to accept part-time contracts, and we wish as an Association to bring this and other anomalies to the attention of the Review Body at the first opportunity

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We hope that consultants and specialists who are not members of the Regional Hospitals' Consultants and Specialists Association and who are in sympathy with the views expressed in this letter will communicate with the honorary secretaries

V COTTON CORNWALL
President
JOHN CA
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H A
Honorary

47 Lincoln's Inn Fields
London W C 2

DOES BUERGER'S DISEASE EXIST?

SIR,—Recent editorials [1] [2] have thrown doubts upon the existence of Buerger's disease (thromboangiitis obliterans) and have suggested that it is merely an expression of atherosclerotic disease This is a view that has a number of adherents and has been growing for some years Whilst I would agree that certain of the criteria which have in the past been applied to this condition may be called in question, I think that a more critical examination is desirable before we accept such a conclusion

One of the earliest critics of Buerger's conception was Fisher, [3] whose well-reasoned but cautious paper was largely based on five cases diagnosed as cerebral thromboangiitis obliterans, arising in elderly men who all had severe atherosclerosis The affected small cerebral arteries had the appearance of "white strings", and this Fisher considered to be the result of bland thrombi forming on the distal side of atherosclerotic occlusions The illustrations of these are beautiful examples of the canalisation of propagated clot, with normal veins One is not disposed to quarrel with Fisher's interpretation, or with his conclusion that "cerebral thromboangiitis does not exist", but I doubt if it is legitimate to equate such lesions in non-anastomotic arteries with those of Buerger's disease in the limbs, and to argue for a similar pathogenesis

Discussing the matter, Fisher refers to Lindbom,[4] making the point that in the latter's extensive study of arterial disease in the leg, thromboangiitis should have been observed, which was not the case This does not necessarily follow, since Lindbom's examinations of the cadaver were made on a selection of elderly subjects all over the age of 50, the more elderly being preferred Moreover, in the smaller arteries his pathological examination of the dorsalis pedis did not extend beyond the bases of the metatarsal bones, or of the posterior tibial artery beyond its division into the two plantars He examined 80 of these cases histologically, and it is clear that his main preoccupation was with calcification But in his clinical cases Lindbom refers to 7, all under the age of 40, in which no internal thickening was seen in such arteries as were patent "In these cases the wall factor was, if existent at all, unknown"

Gore and Burrows, who support Fisher, report 3 post-mortem examinations on males between 43 and 55, with extensive atherosclerotic disease and occlusive thrombi of small and medium arteries and occasional venous thrombi They conclude that the "so-called pathognomonic appearance of thromboangiitis obliterans is precisely that of an organised and recanalized thrombus in a muscular artery without intimal or other disease" They seem, however, to imply the possibility of a distinct ætiology, since they quote my own observations [6] on the differences in the vascular pattern in Buerger's disease and atherosclerotic ischæmia They add "The basic lesion is arterial thrombosis which starts distally in small arteries and progresses by means of retrograde extension to the larger proximal channels" This is the converse of Fisher's explanation "Evidence of primary arterial inflammation was not observed Augmentation of the usual response to vasospastic stimuli is suggested as an explanation of the usual localization of the disease to the extremities" This conception is not really a denial of the existence of a Buerger syndrome, and it accepts a special ætiological factor provocative of thrombosis in the smaller vessels of the foot, with proximal progression, though in common with most recent writers the authors reject the inflammatory element which Buerger stressed

The most recent paper is that of Wessler et al, who state

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6 Tidd R H Dible J H Aird I Peripheral Vascular London 1957
S Gurewick V Freiman D G *New Engl J Med*

that no cases of thromboangiitis have been diagnosed in their hospital in the past ten years, and on clinical grounds conclude that the disease does not exist as a separate entity. They also demonstrated, in the legs of cadavers subject to atherosclerosis, and in those amputated for atherosclerotic ischæmia, such changes as thrombosis, inflammation of the arterial wall, associated venous thrombosis and thrombophlebitis, perivascular and perineural fibrosis, &c., all of which have been claimed as evidence of Buerger's disease. In none was "any lesion resembling the acute specific histologic picture described by Buerger found in an artery or vein."

Such, in brief, is the gravamen of the case against Buerger's disease, and the arguments are sufficiently weighty to call for careful consideration. My own view is that the case is far from conclusive. I would agree that certain of the evidence put forward by Buerger (who I do not think from his writings was a very good histologist) is not wholly tenable: for example, his insistence on acute arterial lesions, "pyogenic foci", the alleged specificity of certain histological changes, and the significance of superficial venous lesions. But when all this is accepted there is, in my experience, a group of cases in young males in which the histological changes in the small peripheral vessels of the lower extremity mark them off from the commoner senile (or diabetic) gangrene due to atherosclerosis and thrombosis. Furthermore, these cases have clinical features on which my surgical colleagues diagnose them as thromboangiitis obliterans. The histological difference between these two classes of case is so clearcut that a differentiation can be made with a high degree of accuracy by simply examining sections of digits.

The points of difference are: in the Buerger group the lesions in the small vessels of the extremity are numerous and widespread, and involve both arteries and veins, the picture being one of thrombosis with active canalisation in vessels free from the degenerative changes of advanced life and progressive atheroma. These changes I have illustrated.[6] In atherosclerotic ischæmia, on the other hand, the smaller vessels of the extremity usually escape much damage, thrombosis in them is not common (apart from infective thrombosis in necrosing tissue), and venous alterations are the exception. It is difficult to explain these very real differences except in terms of a different process. If we are asked to assume that atherosclerosis of the proximal vessels is the cause of these peripheral changes, how is it that it produces this peculiar picture of arterial and venous thromboangiitis in the young and not equally in the elderly? It seems reasonable to expect a more efficient collateral circulation in the former and with it a diminished tendency to thrombosis. And yet this is the opposite of what we find. The variations in distribution and severity of senile atherosclerotic lesions in the lower limbs in the aged in both sexes are almost infinite, and yet this does not in my experience of itself produce the peculiar clinical, radiological,[8] and pathological picture which characterises thromboangiitis.

Whilst it may be accepted that the histological descriptions given by Buerger are not wholly accurate, this does not invalidate the whole conception. For this reason it may be as well to discard the eponymous title and to use the term thromboangiitis obliterans for this syndrome, which describes it accurately—at any rate in the lower extremity.

Research Department,
Mount Vernon Hospital
Northwood, Middlesex.
J. HENRY DIBLE

SHINGLES AND CHICKENPOX

SIR,—Your annotation of Nov. 5 interests me as a general practitioner in a rural area which in many aspects is a "remote area". Chickenpox appears in undoubted epidemics, but shingles arises in crops or very small epidemics, and the relationship of chickenpox to shingles can usually be traced. This relationship is indirect, and I believe (without definite proof of course) that the changed infection is not transferred by direct contact, but that an intermediate host is necessary. In other words, the virus of chickenpox or shingles is carried by a healthy carrier, or perhaps more than one, and is manifest as a case of shingles or chickenpox.

This hypothesis is, of course, not invalidated by instances where both shingles and chickenpox arise in the same family, and it would explain the anomalies.

Petworth, Sussex
W. ANTONY BALL

SUICIDE

SIR,—Dr. Casson's observations (Nov. 5) are of considerable medical and social importance, and require urgent and careful consideration.

The attitude to suicide adopted by the Church, and consequently by secular legislation, is not only inconsistent, but has sacrificed the greatest of Christian moral principles, charity, to fortuitous casuistry of very dubious ethical and social value. Although suicide is still regarded in this country, by both Church and State, as a crime (self-murder), there is nothing in the Old and New Testaments to justify such an attitude; while the earliest Patristic writings still allowed, or even approved of, suicide in certain cases, the Church unfortunately came to accept the uncompromising doctrine of Augustine (*De civitate Dei*, i, 16ff.), which interpreted the sixth commandment as including "self-murder" in whatever circumstances.[1 2 3]

With regard to the person who wishes, as Dr. Casson so well observes, "to terminate a life that has become a life-sentence of intractable pain", Thomas More maintained that priests and magistrates should in fact exhort him to put an end to a life which is only a burden to himself and to others. What I believe to be today the prevalent attitude towards suicide has been admirably stated by Westermarck:[3] "But common sense is neither a metaphysician nor a sophist. When not restrained by the yoke of a narrow theology, it is inclined in most cases to regard the self-murderer as a proper object of compassion rather than of condemnation, and in some instances as a hero."

The law as it stands includes the custom, mentioned by Dr. Casson, of presuming (whether for humanitarian or hypocritical reasons) that in such cases "the balance of mind was disturbed"—perjury, as Bentham said, being the penance which prevented an outrage on humanity. The rational and balanced arguments of such men as Thomas More, John Donne, Montaigne, Montesquieu, Voltaire, and Hume (to name but a few) cannot but shake the very foundations of this tenuous Augustinian doctrine of wholesale condemnation of "those sad souls", as Virgil called them, "who in innocence flung away their lives".

In your report on a draft Suicide Bill (Oct. 29), you quote, as a (presumably enlightened) police procedure in cases of attempted suicide today, a statement that "A severe lecture on their stupidity is mostly delivered to the offenders by a senior officer", &c. Those who, through mental or physical illness, intolerable pain and distress, or apparently insoluble emotional or economic difficulties, are driven in desperation to attempt

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[8] Steiner R. in Peripheral Vascular Disorders (footnote 6)

[1] Rose H. J. in Encyclopædia of Religion and Ethics vol. 12, p. 21 Edinburgh 1921

[2] Westermarck E. The Origin and Development of the Moral Ideas vol. 2 p. 229 London 1908

[3] Westermarck E. Christianity and Morals pp. 250–59 London 1939

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7 Wessler S Ming S Gurewick V Freiman D G *New Engl J Med* 1960 23 1149

that no cases of thromboangiitis have been diagnosed in their hospital in the past ten years, and on clinical grounds conclude that the disease does not exist as a separate entity. They also demonstrated, in the legs of cadavers subject to atherosclerosis, and in those amputated for atherosclerotic ischæmia, such changes as thrombosis, inflammation of the arterial wall, associated venous thrombosis and thrombophlebitis, perivascular and perineural fibrosis, &c., all of which have been claimed as evidence of Buerger's disease. In none was "any lesion resembling the acute specific histologic picture described by Buerger found in an artery or vein."

Such, in brief, is the gravamen of the case against Buerger's disease, and the arguments are sufficiently weighty to call for careful consideration. My own view is that the case is far from conclusive. I would agree that certain of the evidence put forward by Buerger (who I do not think from his writings was a very good histologist) is not wholly tenable: for example, his insistence on acute arterial lesions, "pyogenic foci", the alleged specificity of certain histological changes, and the significance of superficial venous lesions. But when all this is accepted there is, in my experience, a group of cases in young males in which the histological changes in the small peripheral vessels of the lower extremity mark them off from the commoner senile (or diabetic) gangrene due to atherosclerosis and thrombosis. Furthermore, these cases have clinical features on which my surgical colleagues diagnose them as thromboangiitis obliterans. The histological difference between these two classes of case is so clearcut that a differentiation can be made with a high degree of accuracy by simply examining sections of digits.

The points of difference are: in the Buerger group the lesions in the small vessels of the extremity are numerous and widespread, and involve both arteries and veins, the picture being one of thrombosis with active canalisation in vessels free from the degenerative changes of advanced life and progressive atheroma. These changes I have illustrated.[6] In atherosclerotic ischæmia, on the other hand, the smaller vessels of the extremity usually escape much damage, thrombosis in them is not common (apart from infective thrombosis in necrosing tissue), and venous alterations are the exception. It is difficult to explain these very real differences except in terms of a different process. If we are asked to assume that atherosclerosis of the proximal vessels is the cause of these peripheral changes, how is it that it produces this peculiar picture of arterial and venous thromboangiitis in the young and not equally in the elderly? It seems reasonable to expect a more efficient collateral circulation in the former and with it a diminished tendency to thrombosis. And yet this is the opposite of what we find. The variations in distribution and severity of senile atherosclerotic lesions in the lower limbs in the aged in both sexes are almost infinite, and yet this does not in my experience of itself produce the peculiar clinical, radiological,[8] and pathological picture which characterises thromboangiitis.

Whilst it may be accepted that the histological descriptions given by Buerger are not wholly accurate, this does not invalidate the whole conception. For this reason it may be as well to discard the eponymous title and to use the term thromboangiitis obliterans for this syndrome, which describes it accurately—at any rate in the lower extremity.

Research Department
Mount Vernon Hospital
Northwood, Middlesex

J. HENRY DIBLE.

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[8] Steiner, R. *in* Peripheral Vascular Disorders (footnote 6).

SHINGLES AND CHICKENPOX

SIR,—Your annotation of Nov. 5 interests me as a general practitioner in a rural area which in many aspects is a "remote area". Chickenpox appears in undoubted epidemics, but shingles arises in crops or very small epidemics, and the relationship of chickenpox to shingles can usually be traced. This relationship is indirect, and I believe (without definite proof of course) that the changed infection is not transferred by direct contact, but that an intermediate host is necessary. In other words, the virus of chickenpox or shingles is carried by a healthy carrier, or perhaps more than one, and is manifest as a case of shingles or chickenpox.

This hypothesis is, of course, not invalidated by instances where both shingles and chickenpox arise in the same family, and it would explain the anomalies.

Petworth, Sussex.

W. ANTONY BALL.

SUICIDE

SIR,—Dr. Casson's observations (Nov. 5) are of considerable medical and social importance, and require urgent and careful consideration.

The attitude to suicide adopted by the Church, and consequently by secular legislation, is not only inconsistent, but has sacrificed the greatest of Christian moral principles, charity, to fortuitous casuistry of very dubious ethical and social value. Although suicide is still regarded in this country, by both Church and State, as a crime (self-murder), there is nothing in the Old and New Testaments to justify such an attitude: while the earliest Patristic writings still allowed, or even approved of, suicide in certain cases, the Church unfortunately came to accept the uncompromising doctrine of Augustine (*De civitate Dei*, i, 16ff.), which interpreted the sixth commandment as including "self-murder" in whatever circumstances.[1] [2] [3]

With regard to the person who wishes, as Dr. Casson so well observes, "to terminate a life that has become a life-sentence of intractable pain", Thomas More maintained that priests and magistrates should in fact exhort him to put an end to a life which is only a burden to himself and to others. What I believe to be today the prevalent attitude towards suicide has been admirably stated by Westermarck:[3] "But common sense is neither a metaphysician nor a sophist. When not restrained by the yoke of a narrow theology, it is inclined in most cases to regard the self-murderer as a proper object of compassion rather than of condemnation, and in some instances as a hero."

The law as it stands includes the custom, mentioned by Dr. Casson, of presuming (whether for humanitarian or hypocritical reasons) that in such cases "the balance of mind was disturbed"—perjury, as Bentham said, being the penance which prevented an outrage on humanity. The rational and balanced arguments of such men as Thomas More, John Donne, Montaigne, Montesquieu, Voltaire, and Hume (to name but a few) cannot but shake the very foundations of this tenuous Augustinian doctrine of wholesale condemnation of "those sad souls", as Virgil called them, "who in innocence flung away their lives."

In your report on a draft Suicide Bill (Oct. 29), you quote, as a (presumably enlightened) police procedure in cases of attempted suicide today, a statement that "A severe lecture on their stupidity is mostly delivered to the offenders by a senior officer", &c. Those who, through mental or physical illness, intolerable pain and distress, or apparently insoluble emotional or economic difficulties, are driven in desperation to attempt suicide, and pitifully have failed, are surely in need of the greatest possible assistance (inadequate as it may well be) of physical and psychological medicine, and expert social services "a severe lecture on their stupidity" (*whose* stupidity?)—it may be supposed, to "bring them to their senses"—would seem not only superficial, pharisaic, presumptuous, and insulting to human intelligence and suffering, but as futile as the so-called remedies for the psychotic patient, to which Cælius Aurelianus (*On Chronic Diseases*, I, 5) referred somewhat ironically "Some say he should be flogged, apparently so that he may regain his sanity by a kind of whipping of his reason" Our present laws on suicide are indeed reminiscent of the words of the judge, in Samuel Butler's *Erewhon* "You may say that it is your misfortune to be criminal, I answer that it is your crime to be unfortunate"

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[1] Rose, H. J. *in* Encyclopædia of Religion and Ethics; vol. 12, p. 21. Edinburgh, 1921.

[2] Westermarck, E. The Origin and Development of the Moral Ideas; vol. 2, p. 229. London, 1908.

[3] Westermarck, E. Christianity and Morals; pp. 250–59. London, 1939.

The position on suicide adopted by the Church would appear to be morally and socially untenable, and, it may be hoped, will soon be legally unenforceable, from the medical and psychiatric point of view, it is absolutely inadmissible Apart from being archaic in the light of contemporary medical and sociological advances, these ecclesiastical and secular laws and practices are based on bad theology what, indeed, do they make (with their "unbalanced mind" mythology—if no longer requiring a burial at the crossroads) of those noble individuals who deliberately give their lives for their principles, their country, their family, and those whom they love? How, indeed, can their narrow and uncompromising attitude to suicide be reconciled with such high ethical concepts as these (*John*, x, 11, xv, 13) "the good shepherd giveth his life for the sheep", "greater love hath no man than this, that a man lay down his life for his friends"?

Bransgore, Hampshire R H AHRENFELDT

STRONTIUM TURNOVER

SIR,—In the interesting article by Dr Widdowson and her colleagues (Oct 29) there is an error in relation to our strontium test of bone turnover in man[1] We have used stable and not radioactive strontium, because we are not certain of the safety of introducing bone seeking radioactive isotopes into the human body

Postgraduate Medical School,
London, W 12

RUSSELL FRASER
MICHAEL HARRISON

THE BORDERLINE FOR SEVERE SUBNORMALITY

SIR,—In their letter of Oct 29, Dr MacMahon and Dr Clarke suggest that in the memorandum on parts I, IV–VII, and IX of the Mental Health Act, the Ministry of Health have taken the view that the borderline between subnormality and severe subnormality comes at I Q 70, or even rather higher

As your correspondents point out, the Royal Commission on the Law relating to Mental Illness and Mental Deficiency considered that the test of severe subnormality should be the patient's inability to live an independent life, and they suggested that, using this criterion, it would very often be found that a patient with an intelligence quotient below the 50–60 level should be classified as severely subnormal My understanding of the Mental Health Act is that the definitions of subnormality and severe subnormality in section IV are based directly upon the views expressed by the Royal Commission, and I cannot find anything in the Ministry's memorandum which in any way contradicts this view As I read it, the passage referred to by Dr MacMahon and Dr Clarke merely indicates—as is surely the case—that many patients who will be classified as subnormal show both intellectual defectiveness and emotional instability The fact that the words intellectually dull were used was not, I am sure, meant to imply that the division between the subnormal and the severely subnormal should be regarded as coming at some other point than that suggested by the Royal Commission

Abinger Hammer,
Dorking

W REES THOMAS

ORAL TREATMENT OF PERNICIOUS ANÆMIA WITH LOW DOSES OF H P P /1

SIR,—There is good reason to suppose that all the stores of vitamin B_{12} in the body are connected This is supported by the finding of Ross and Mollin[1] that there is a similar organ distribution in normal and in deficient subjects, and also by various observations showing that in vitamin-B_{12} deficiency the B_{12} level is decreased to about the same extent in the various "subpools", such as liver, bone-marrow, and circulating blood[2] This being so, a low vitamin-B_{12} serum level indicates a low total pool If Dr Mooney and Dr Heathcote (Nov 5) believe that their vitamin-B_{12}-peptide complex is absorbed better than ordinary crystalline vitamin, then in view of the subnormal or low serum-B_{12} levels one would be inclined to suggest that either it is quickly re-excreted in the urine or that an unusually large proportion of the vitamin is shifted to the tissues

We suggest that Dr Mooney and Dr Heathcote carry out microbiological B_1 serum assays on some of their patients treated with H P P /1, discontinue treatment, and establish the rate of decline of the B_{12} levels and also the interval before megaloblastic erythropoiesis recurs Having done this, they may then conclude that with the doses they recommend they were unable to build up a satisfactory body pool of the vitamin This will probably also give the answer to their insistence on having our explanation of the serum-B_1 levels *on this particular form of therapy* There is a difference between the minimum effective maintenance dose (0 5–1 0 μg of vitamin B_{12} per day) and the dose required for the building up of a more than minimum body pool

For our part we, like Dr Shinton (Nov 5), are satisfied that "as a general concept of rational therapy" 200 μg or more daily would have to be given

City General Hospital
Sheffield

S VARADI
A ELWIS

SIR,—After the interesting exchanges between Dr Mooney and Dr Heathcote and Dr Varadi, might I venture to suggest that the argument is pointless?

Scientifically, it seems to have been established that the vitamin-B_1 /peptide has destroyed the concept of Castle's intrinsic factor and changed our thinking in this respect, but the long-term oral treatment of pernicious anæmia by this compound must remain an unknown quantity irrespective of the serum-B_1 levels

I assume that patients maintained on this therapy have had it carefully explained to them that the treatment is new, the long-term effects unpredictable, and the prognosis consequently doubtful Furthermore, that this treatment is being used instead of a proven method that can guarantee (in adequate dosage) no ill-effects from involvement of the central nervous system Also, to ensure that subtle irreversible damage is not being produced either in the cerebrum or spinal cord, that these patients are being subjected to a complete neurological survey at least once a month This survey must include examination of the visual fields and an electroencephalogram

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[1] Fraser R Harrison M Ibbertson K *Quart J Med* 1960 29 85

[1] Ross G I M Mollin D L Vitamin B_{12} in Tissues in Pernicious Anæmia and Other Conditions p 437 Stuttgart 1957

[2] Gräsbeck R *Scand J clin Lab Invest* 1959 11, 250

Provided these standards are adhered to there seems only a very slight risk in maintaining patients on oral B_{12} peptide. In my opinion, however, it is exceedingly doubtful whether there will ever be a place for this form of treatment in the alleviation of pernicious anæmia and or subacute combined degeneration of the cord Even if the patients preferred frequent pills to infrequent injections I am sure that most doctors would prefer to know that the vitamin B_{12} was firmly secured in two or three inches of muscle

Institute of Clinical Research
Middlesex Hospital Medical School,
London W 1

A D M SMITH

NATURE OF ESSENTIAL HYPERTENSION

SIR,—We wish to comment on two of the statements made by Dr Morrison and Professor Morris (Oct 15) in relation to their study of London busmen

(1) They state that "the drivers whose parent(s) died in middle age showed a bimodal distribution of blood-pressure" In fact, they showed a bimodal distribution of systolic blood-pressures only Diastolic pressures were unimodal and, as we showed earlier[1] their argument for hidden bimodality was based on a statistical artefact.

(2) They repeat their claim that there is more hypertension among the offspring of parents who die in middle-age than among the offspring of parents who die late and this claim forms the basis of their whole study In fact as the following figures show, the mean pressures of the two groups of drivers are almost identical

	Mean pressure of drivers	
	Systolic	Diastolic
(a) Group with a parental death in middle age (n = 90)	153·7	89·7
(b) Group where both parents survived to old age (n = 95)	152·2	88·4

National Institute of Arthritis
and Metabolic Diseases,
Bethesda, Maryland.

HARRY KEEN

Department of Epidemiology
Johns Hopkins University
School of Hygiene and Public Health,
Baltimore.

GEOFFREY ROSE

DIAGNOSIS OF DIABETES

SIR,—Dr Freeman (Oct. 29) is surprised at my finding[2] that 48% of a group of diabetics in Dundee had had continuous diabetic symptoms for more than four months and that 20% had noted these for at least a year before the diagnosis was made He contrasts these findings with corresponding figures of 27% and 15% in his Exeter survey[3]

I suggest that there is no need for surprise because the 352 diabetics I studied and the 300 investigated by Dr Freeman were dissimilar in a variety of ways

His patients were restricted to those diagnosed in the years 1952 to (presumably) 1957 and attending one particular hospital, whereas mine are what I believe to be a representative cross-section of known diabetics in the Dundee area. In addition my series differed in age at onset and included a much higher proportion of females—particularly post-menopausal females This latter group is, of course, especially prone to the slow insidious type of onset, which may partly account for the differences in our results

It would I agree, be unwise to suggest that my findings necessarily apply to all British diabetics and I have never claimed this I can merely claim them to be typical of known diabetics in the Dundee area. Similarly, Dr Freeman's own results can properly be applied only to a selected group of diabetics in a particular part of Devon Even if he and I had used similar methods of sampling, the figures for Dundee and for Exeter need not necessarily be identical The two populations may well be dissimilar in dietary habits There may be differences between females in the areas both in reproductive histories and in anthropometric characteristics For these and other reasons the epidemiological patterns of diabetes in Dundee and in Exeter might differ and this could have an effect on the type of onset.

The other matters raised by Dr Freeman are interesting, as was his original paper on the subject I should like to comment on his figures in the light of my own findings but, once again, comparison may be misleading because of different methods of selection and classification I hope in due course to publish the full results of my studies with details of the criteria used.

Meanwhile may I emphasise the deficiencies in our knowledge of the true epidemiology of diabetes mellitus throughout Britain. Most reports dealing with the subject refer only to known diabetics and, in particular to those on the books of hospital diabetic clinics There are signs that professional and public interest in the early detection of the disease is now increasing Until there is general agreement on the importance of searching for hitherto undiagnosed diabetics instead of waiting until they present themselves after months or years of symptoms, our epidemiological knowledge will remain inadequate

I found Dr Freeman's statement that 15% of his diabetics had had symptoms for a year or more before being diagnosed to be little more reassuring than my finding of 20% If either figure were applicable to the country as a whole, it would represent a vast amount of needless human suffering For that reason, I welcome your leading article (Oct. 1) as yet another reminder of the importance of adopting a more vigorous policy towards diabetes detection

Ravensthorpe Northants

J J A REID

BROADER MEDICAL TEACHING

SIR,—I should like to support every word of Dr Cardew's letter of Nov 5 As a consultant, who started as a G.P.-surgeon, I can speak from some personal experience. My basic training in general practice has been more than useful.

The man entering general practice has received no teaching on the treatment of the minor ills of this life As such conditions constitute the bulk of his practice any ideas on treatment from the advertisers are of course gratefully received. Unfortunately the mere prescription of some new drug or form of support is but a minor part—if a part at all—in the treatment of many of these conditions I have discussed this at some length in a treatise on my own specialty in general practice[1]

Many in the profession (consultants included) are now content to be mere tradesmen recommending advertised goods Only by a better training can we set our house in order and maintain a true professional standard.

Tunbridge Wells

W H GERVIS

SIR,—The medical student does not expect the gynæcologists to teach him about eyes nor does he expect hospital consultants and registrars to instruct him in general practice It is by attending patients with a good family doctor that the would-be general practitioner can learn his work quickly Experience gained at first hand by a G.P. trainee must far outweigh vicarious experience handed out by a hospital specialist who has, perhaps against his better judgment, spent six months in compulsory general practice

Dr Cardew suggested (Nov 5) that every future teacher in the hospital service should, between the appointments of registrar and senior registrar, spend four consecutive periods of six weeks attached to each of four different types of general practice (industrial, semi-urban rural and seaside) I fail to see how this would effectively broaden medical teaching, or who could gain from such a plan

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1 *Lancet* 1959 ii 1028
2 Reid J J A *Med Offr* 1960 103 325
3 Freeman A G *Brit med J* 1958 i 1149

1 Orthopædics in General Practice Is It Rheumatism Doctor? London 1958

The limited time spent in each type of practice would not give anyone the opportunity of appreciating for himself that especial satisfaction found in giving medical care to the same people over a period of years, or even over several decades

The only registrars enjoying the experience would be those least in need of that experience—those who already have wide interests, including an understanding of their fellow men The registrars who would consider the half-year in general practice as time wasted, perhaps because they are already engaged in some research project in their own specialty, could gain little other than a feeling of frustration

The patient could derive no benefit from the plan, for he likes to consult the practitioner whom he knows and who knows him If, on the other hand, the future hospital teacher is present only as an observer, who would pay his salary?

London, S E 4 MARY RESTELL

HEALTH OF EXECUTIVES

SIR,—Our Health Conference for Business Executives fixed for Nov 24 in the Royal Festival Hall is arousing considerable interest Some doctors are asking "But why business executives? Do we not all need health education?"

The triumphs of preventive medicine are chiefly in childhood and youth It has still to make its impression on the afflictions of middle-age Men and women who bear stress and responsibility need health education badly, and not only from the personal point of view Their decisions can influence the health and fitness of large numbers of employees

This is the main reason for the conference, which merely continues what the Chest and Heart Association has been doing for sixty years We have always encouraged the participation of laymen in our meetings, and this policy has been well worth while

This year, President Eisenhower's physician, Dr Paul Dudley White, pays us the compliment of coming over specially to speak on coronary thrombosis

HARLEY WILLIAMS
London, W C 1 Secretary General, Chest and Heart Association

BINDING BOOKS

SIR,—Your review (Nov 5) of *Lectures on Hæmatology*, edited by F J G Hayhoe, suggests that this book and others in the same series might well be published "in a less expensive form—say, paperback with plastic binding and without some of the illustrations" The point about the illustrations is being considered by our editorial office, but the rest of the suggestion is based on a persistent fallacy which bedevils all discussions about book prices and really ought now to be discarded

To bind a book in paper instead of in a hard binding produces a quite insignificant economy In paper the *Lectures on Hæmatology* might be retailed at 58*s* 6*d* instead of 60*s*, its price in hard covers (The use of the thermoplastic process instead of stitching is only possible if a minimum of 5000 copies are bound at one time, and even this would not save more than another shilling) The thing, and the only thing, that makes a paperback (in *the modern sense) cheap is that it is printed in enormous* quantities at a time The readers of a technical work, such as the *Lectures on Hæmatology*, must be strictly limited however cheap its price

R W DAVID
Manager
London, N W 1 Cambridge University Press

PROGNOSIS AND PROPHYLAXIS AFTER CORONARY OCCLUSION

SIR,—Professor McMichael and Dr Parry's magnificent summary (Nov 5) of the case against anticoagulants will no doubt stimulate a number of powerful counterblasts This does seem to be a subject which has produced as much statistical prestidigitation and high feeling as any—probably because of the absence of any other prophylactic treatment for the disease, the difficulties and dangers of the treatment, and maybe because of disappointed expectations of the results of treatment It is natural to seize on this only hope of doing something to prevent recurrence of such a dread disease In addition, anybody who has experience of the treatment will know how quickly patients come to believe that it is lifesaving—a belief which the doctor often fosters, both to justify the dangers involved, and also to induce the necessary discipline which will reduce these dangers and make the treatment better "controlled" One overstates the case, and then desperately hopes the overstatement will be proved to be right On the other hand, if the patient is *not given the treatment there is a sneaking feeling that he may be being denied his only chance* It is hard to imagine a more guilt-producing situation!

It seems to me that too much has been expected of anticoagulants in the treatment of ischæmic heart-disease and the prophylaxis of myocardial infarction In this disease atherosclerosis causes progressive narrowing of the coronary arteries with or without thrombosis in them As the narrowing proceeds collateral vessels develop These processes cause gradual myocardial degeneration punctuated by acute episodes of myocardial infarction These episodes are usually the result of coronary thrombosis, but may not be The relative importance of these various factors in the disease will vary from patient to patient In young patients atherosclerosis will be *less far advanced, and thrombosis will be relatively more important In older, diabetic, hypertensive, and fat patients atherosclerosis may be expected to be the more important factor* Similarly, patients who have evidence of widespread myocardial disease such as heart-failure, hypotension, arrhythmias, enlarged heart, and recurrent infarction (the so-called bad-risk cases) are those who may be expected to have widespread coronary atherosclerosis (Bjerkelund's [1] cases with a "high force of recurrence" presumably come into this group)

Parallel with this varying pathological picture it is found clinically [2] that young patients are more likely to have serious infarcts (presumably because collaterals have not had time to develop), but if they make an uncomplicated recovery they have a good prognosis (because their myocardium is healthy), and are more likely to die of a further infarction Conversely older and bad-risk patients have less serious infarcts (because collaterals have had time to develop), but are more likely to die of myocardial failure, and have a worse prognosis

Anticoagulants are likely to be most effective in preventing coronary thrombosis, and to have little or no effect on progress of atherosclerosis Prophylaxis may be expected therefore to be most effective in those patients in whom thrombosis plays the greater part—i e, in young good-risk cases This is what has been found in both Bjerkelund's [1] and the Medical Research Council [3] trials Thus, the M R C reported a *fivefold* reduction in recurrent infarction in their treated group, and the improvement lasted for at least two years *In spite of this* the reduction in mortality was only about *one half*, and that only during the first six months *of treatment* This is most mysterious *because reinfarction is much the commonest cause of death in this age-group* In Honey and Truelove's young patients the incidence was 75% The answer may lie in the vexed question of the diagnosis of reinfarction There may have been unwillingness to diagnose reinfarction in the treated group unless the patient actually died this would have the effect of increasing the apparent mortality of, and the apparent reduction of, reinfarction Bjerkelund's figures show a much closer correlation between reduction of reinfarction and mortality in his treated group of young patients, the incidence being two-fifths and four-sevenths respectively He was more definite about his diagnosis of reinfarction and also had a much more complete postmortem follow-up His postmortem studies did show that the incidence of coronary thrombosis in patients who died of recurrent infarction was halved by anticoagulant treatment

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[1] Bjerkelund C J *Acta med scand* 1957 158 suppl 330
[2] Honey G F Truelove S C *Lancet*, 1957 i 1209
[3] *Brit med J* 1959 i 83

Thus, both these series do show a certain reduction in the reinfarction-rate Bjerkelund's postmortem studies do provide direct evidence that anticoagulants can reduce the incidence of coronary thrombosis as the cause of the reinfarction On the other hand, the absence of a reduction in mortality after at the most a year shows that there is inexorable progression of the atherosclerosis, in spite of treatment More and more patients must go on to the stage of widespread arterial disease and myocardial degeneration, in which anticoagulants cannot be expected to be so helpful, and die of heart-failure, or they may die a sudden death (sudden death without infarction is commonest in sclerosis alone [4]) In addition to the reduction in coronary thrombosis Bjerkelund did find a reduction in mural thrombosis in his treated patients at postmortem Although Gilchrist and Tulloch [5] found little difference in mural thrombosis, there was a reduction in systemic emboli in their series

I believe that there is a case for long-term prophylactic treatment of coronary-artery disease with anticoagulants It is not possible to say for certain in the individual patient what relative parts thrombosis and sclerosis have played and will play in the development of the disease, although likelihoods can be assessed on the grounds described above The greater the part thrombosis plays, the more valuable is treatment likely to be Patients should be reviewed every six months, and any who are developing signs of widespread myocardial disease can be rejected, particularly those whose treatment is difficult to control Those with no such signs can be continued on treatment Possibly unconscious selection along these lines is what has produced such favourable results in some series Patients who present with angina or acute coronary insufficiency should be treated in the same way Postmortem evidence shows that both these symptoms may be associated with coronary thrombosis, and indeed the good effect of anticoagulants in acute coronary insufficiency in preventing definite infarction [6] is further indirect evidence that they can prevent the spread of coronary thrombosis The prognosis of patients presenting with angina is the same as those presenting with infarcts,[7] and logically they should be assessed for treatment in the same way

There is a tendency for all-or-none opinions to be held about this treatment Perhaps the best course is careful selection of patients for treatment, the length of which should be suited to the individual patient If patients are not led to believe that treatment is lifesaving, stopping it will be easier

University College Hospital
London, W C 1

P M S GILLAM

SIR,—The paper by Professor McMichael and Dr Parry (Nov 5) is refreshing to those, like myself, who think that the case for long-term and possibly even immediate treatment with anti-prothrombin agents in coronary thrombosis is not yet proven

The paper should help to prevent abuse of such therapy At present, some physicians give it in virtually all cases of coronary thrombosis and angina of effort on a long-term basis not to do so, they feel, may be to the detriment of their patients Anticoagulant clinics have sprung up in many hospitals, dealing with hundreds and sometimes with a thousand or more cases, and I have heard of a pathologist who spent a considerable part of his day in the estimation and advice on these tests What is really required is follow-up—whenever possible, of large series over ten years or more—of cases treated with or without anti-prothrombin agents

A surgeon who has carried out major surgery on patients receiving anti-prothrombin agents assures me that there was no abnormal tendency to hæmorrhage in these cases This is difficult to understand in view of the alleged value of such drugs in preventing clotting, yet it need not be so surprising, since it is recognised that the clotting-time in patients on anti-prothrombin agents, despite prolonged prothrombin-time, may be quite normal There need not therefore be any correlation between prothrombin-time and clotting-time The position may be different with heparin, which prolongs the clotting-time, but at present no oral heparin or heparinoids are available, and long-continued therapy with these drugs is therefore not feasible

It seems to me that we should adopt a more guarded attitude, and not allow ourselves to believe that we should be failing in our duty to our patients if we did not use anti-prothrombin agents in every case of angina pectoris and coronary thrombosis

St Mary Abbot s Hospital,
London, W 8

B GOTTLIEB

ETHIONAMIDE

SIR,—Your leading article of Oct 29 mentioned the trials which are being carried out by the research committee of the British Tuberculosis Association in which this drug is used for the treatment of patients with advanced pulmonary tuberculosis in whom previous treatment with streptomycin, isoniazid, and P A S has failed You stated in error that in these trials a group of patients is being treated with ethionamide and cycloserine, in fact, this combination is not being used

The reasons for not using this combination were provided by the results of a preliminary trial reported by Riddell, Stewart, and Somner [1] in which patients were given ethionamide 0 5 g daily with either cycloserine 0 5–1 g daily or pyrazinamide 2–3 g daily (according to body-weight) This dose of cycloserine appeared inadequate to protect completely against the emergence of cultures with decreased sensitivity to ethionamide Increase in the dose of cycloserine was not thought to be practicable because of its side-effects, so that the combination of cycloserine with ethionamide alone is not used in the present trial

On the other hand, in the preliminary trial [1] the dose of ethionamide (0 5 g) appeared insufficient completely to prevent decrease of pyrazinamide sensitivity In view of this in the present trial the recommended dose of ethionamide has been increased to 1 g daily in combination with pyrazinamide A second group of patients is being treated with ethionamide (1 g daily) with pyrazinamide and cycloserine, to see if this combination will prevent the emergence of resistance to these drugs Patients are being allocated at random to these two treatment groups (i e , either ethionamide plus pyrazinamide, or ethionamide plus pyrazinamide and cycloserine) In addition a separate trial is in progress to study treatment with ethionamide and streptomycin in patients whose organisms are thought to be resistant to isoniazid and P A S

The British Tuberculosis Association Research Committee share the hope expressed in your article that these controlled cooperative investigations will eventually provide much information of value for treating those in whom initial treatment has failed Should your readers in Great Britain have patients they would like included in the trial, I would be pleased to send them a protocol

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[4] Yater W M et al *Amer Heart J* 1948 36 334 481 683
[5] Gilchrist A R Tulloch, J A *Scot med J* 1956 1, 1
[6] Wood, P Diseases of the Heart and Circulation London 1956
[7] Seims E. *Acta med scand* 1960 166 255

[1] Riddell, R. W , Stewart, S M , Somner, A R *Brit med J* 1960, ii 1207

K M CITRON

Institute of Diseases of the Chest,
Brompton, London, S W 3

Coordinator, British Tuberculosis
Association Ethionamide Trial

*** We are grateful to Dr Citron for correcting our mistake —ED L

SPORTS MEDICINE

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Via Antonio Serra, 104,
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Secretary General
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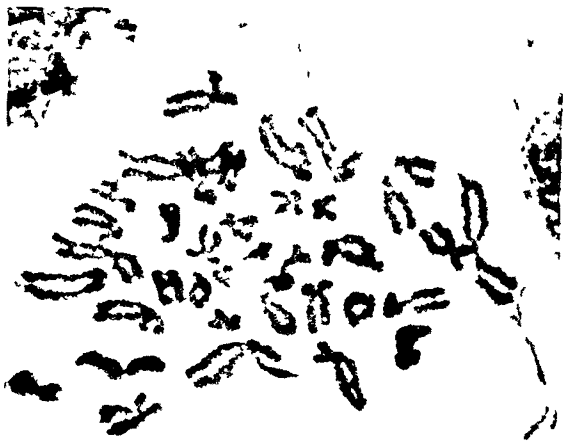

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Ferndown Dorset S F DURRANS

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The traffic in London becomes more and more congested every day and the stress of driving is proportionately increased I am sure this stress and accompanying exhaustion, especially during the peak hours in London, is a cause of many coronary thromboses But exhaust fumes may contain vasoconstrictor substances that act as a substantial contributory factor In view of present-day conditions, I do not support the suggestion that driving can be a form of relaxation

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This case showed a combination of several factors dehydration after diarrhœa and exposure to a hot dry climate without sufficient intake of fluid, aggravated by an increased dose of hydrochlorothiazide, combining to induce dangerous hypotension

Similar reactions, though not as dramatic, were seen lately in two other patients, also new arrivals from abroad and not yet mittee share the hope expressed in your article that these controlled cooperative investigations will eventually provide much information of value for treating those in whom initial treatment has failed Should your readers in Great Britain have patients they would like included in the trial, I would be pleased to send them a protocol

K M CITRON

Institute of Diseases of the Chest,
Brompton, London, S W 3

Coordinator, British Tuberculosis
Association Ethionamide Trial

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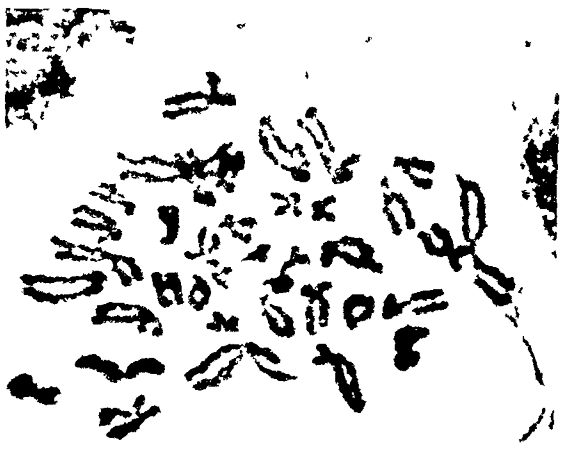

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acclimatised, who kept to their former doses of hydrochlorothiazide

For many years it has been known in this country—before the start of oral diuretic treatment—that regular mersalyl injections had to be stopped when the khamseen blows (a hypotensive agent in itself) Doctors who know that patients on hypotensive drugs intend going abroad should warn them to be careful in an unfamiliar climate

Haifa Israel H W BRUNO

TREATMENT OF FANCONI'S ANÆMIA

SIR,—Interest in the treatment of this condition has been reawakened by a report [1] of the use of a combination of testosterone and prednisone in aplastic anæmia in children The bone-marrow regenerated in 4 out of 5 cases so treated, and 1 of these was a Fanconi's anæmia Later figures indicated moderate to full remission in 11 out of 17 cases on this treatment 3 showed no response and 3 died in the early stages of treatment [2]

It was decided to try this treatment in Cape Town in a brother and sister with Fanconi's anæmia The disease and its occurrence in 5 children seen here has been described elsewhere [3] 3 of the 5 patients were members of one family, which included the 2 children and an elder sister who died of the disease in 1957

CASE 1—A boy, aged 7 years, was first seen by us in 1959 and was found to have Fanconi's anæmia The anæmia was not severe, but he had associated thrombocytopenia and neutropenia with a hypocellular marrow and several congenital defects Treatment with methyl testosterone (25 mg daily) and prednisone (10 mg daily) began in January, 1960 After 3 months his hæmoglobin, though not showing a spectacular rise, was nevertheless maintained without transfusion during this time He had previously had two transfusions over a period of 5 months (fig 1) He also had a platelet and a neutrophil response The platelets, which had varied between 50,000 and 70,000 per c mm, had risen to over 100,000 and his neutrophils from between 2% and 34% to 66% The previously hypocellular marrow showed considerable activity, particularly of red-cell precursors

CASE 2—A girl, 11 years old, first came to us a few months before her brother and the initial diagnosis was aplastic anæmia When the brother was seen and his congenital defects observed, the girl was re-examined and found to have deficient thenar muscles on one hand as well as some pigmentation which had not previously been appreciated Her peripheral blood showed essentially the same features as the boy, but to a greater degree She had several marrow aspirations and one trephine of the iliac crest, and all showed very defective marrow activity She required four transfusions at intervals of approximately 2 months

Treatment also began in January, 1960—prednisone (10 mg per day) and methyl testosterone (50 mg per day, 2 mg per kg per day in each child) 3 months later (April 1, 1960) her hæmoglobin had risen from 9 8 g to 13 1 g per 100 ml and she had needed no transfusions during this time (fig 2) Her bone-marrow also showed erythropoietic activity and both platelets and neutrophils were rising from their previously low levels

In Shahidi and Diamond's patients the first response was always in the red-cell series and the other blood elements showed signs of regeneration later It was usually 2–3 months before benefit was seen, so that in our cases we may find a further increase in platelets and neutrophils later

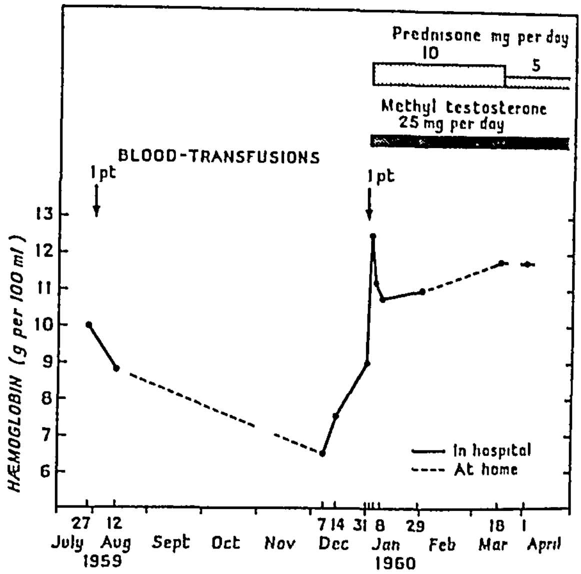

Fig 1—Hæmoglobin levels in case 1, a boy of 7

Side-effects in both children so far have been slight acne, some flushing, and "Cushing" appearance, and both have developed pubic hair In addition, the boy has shown some enlargement of the external genitals They both feel very well, have large appetites, and are no longer easily fatigued

Because of the Cushing effects the dose of prednisone has been reduced to 5 mg daily in each case and there has been some decrease in the children's weights In view of the genital overgrowth in the boy, it may be desirable to reduce the dose of methyl testosterone, but for the present it is being kept at the starting level

The results, especially in the girl, seem promising, but more than this cannot yet be claimed According to Shahidi and Diamond,[1] therapy will have to be continued for at least another 6 months, and it remains to be seen whether the improvement will thereafter be maintained without treatment It is not yet known whether further courses of the drugs are necessary or not This will depend on follow-up studies of peripheral blood and bone-marrow

The future may show that complete recovery is sometimes possible from this hitherto fatal disease

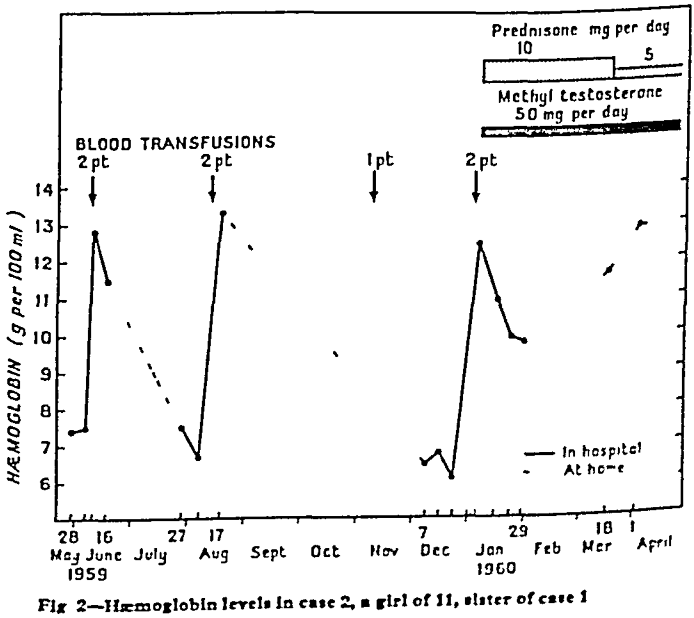

Fig 2—Hæmoglobin levels in case 2, a girl of 11, sister of case 1

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[1] Shahidi N T, Diamond L K A.M.A J Dis Child 1959 98 293

[2] Diamond L K Personal communication, 1959

[3] McDonald R, Goldschmidt B L Arch Dis Childh (in the press)

Addendum —At the end of June, 1960, these children had been under treatment for 6 months, and in each case the hæmoglobin was over 13 g per 100 ml Bone-marrow activity was likewise satisfactory In view of the good response to treatment, both drugs have been reduced in amount, and it is intended to discontinue therapy in a month or two The blood-picture will thereafter be watched

Thanks are tendered to Prof F J Ford for advice and Dr J G Burger, superintendent of Groote Schuur Hospital, for permission to publish this report, which is based on a paper presented to the 4th Congress of the South African Pædiatric Association in Cape Town on April 4, 1960

Department of Child Health,
University of Cape Town, and
Groote Schuur Hospital,
Observatory, Cape Town. ROBERT MCDONALD

POSTPARTUM PRE-ECLAMPSIA

SIR,—May I congratulate Flight-Lieutenant McFadyen on observing and describing the phenomena recorded as " postpartum pre-eclampsia " in your issue of Nov 5? He will forgive me for pointing out that I did mention that such events do occur on pp 164 and 243 of my book, *The Pregnancy Toxæmias*, and for the first time in your columns in 1932 [1]

Would it not be wiser to attribute all the " eclampsias " to disturbances in one or more of the homœostatic mechanisms rather than postulate a single cause for one or all of them?

Bradford. G W THEOBALD

PERITONEAL SPLASH A PHYSICAL SIGN

SIR,—The letters by Mr Lane Roberts (Sept 24) and Mr Smiddy (Oct 15) interested me, particularly because I have found it useful to try to elicit the presence of fluid in doubtful perforation

My custom in such doubtful cases is to auscultate the abdomen for bowel sounds, and the patient is asked to cough If there is fluid and air in the abdomen then a double sound is heard as the wave of fluid is displaced by contraction of the diaphragm The nearest English equivalent I can suggest is " tch-tch " When this is heard one can be confident that there is air and fluid in the abdomen, but it is not heard in every case, particularly in early perforation when there may be little fluid

Weymouth and District Hospital J JEWERS

PULLED SHORT EXTENSORS

SIR,—I should like to describe briefly a new differential diagnosis of twisted ankle or foot—" pulled short extensors "

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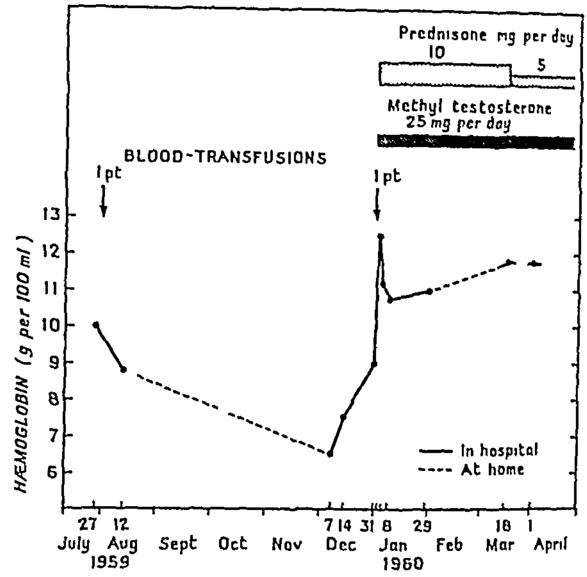

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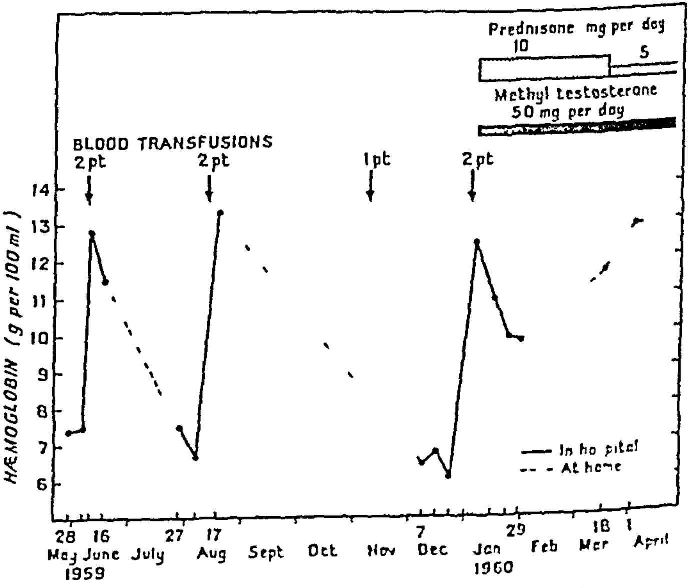

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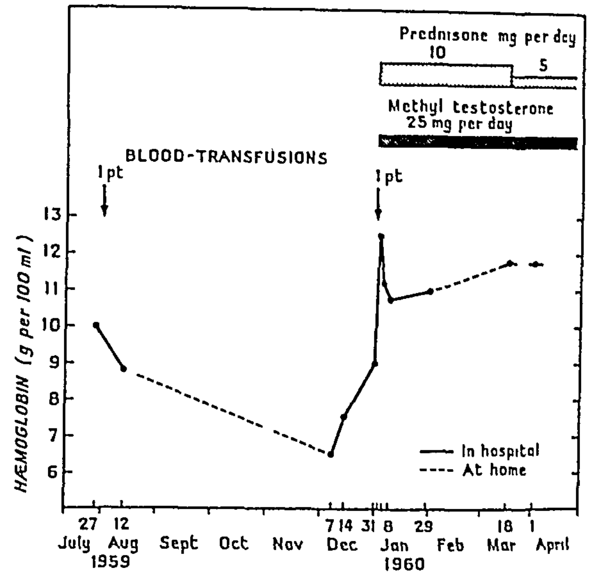

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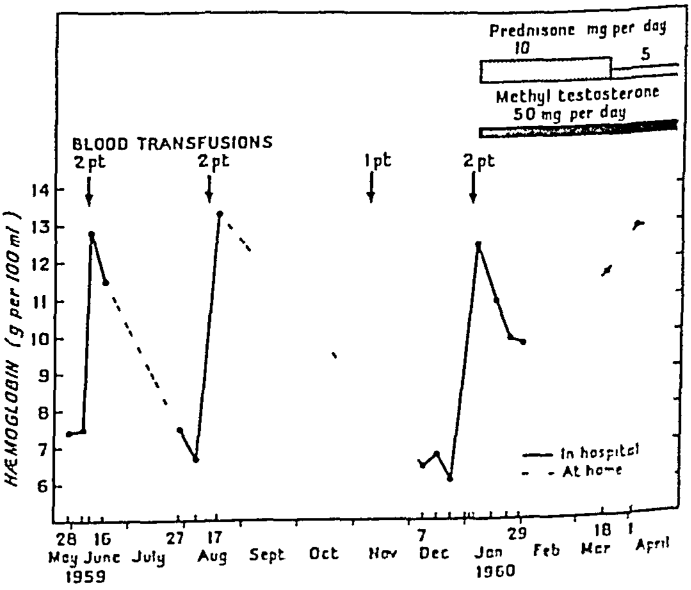

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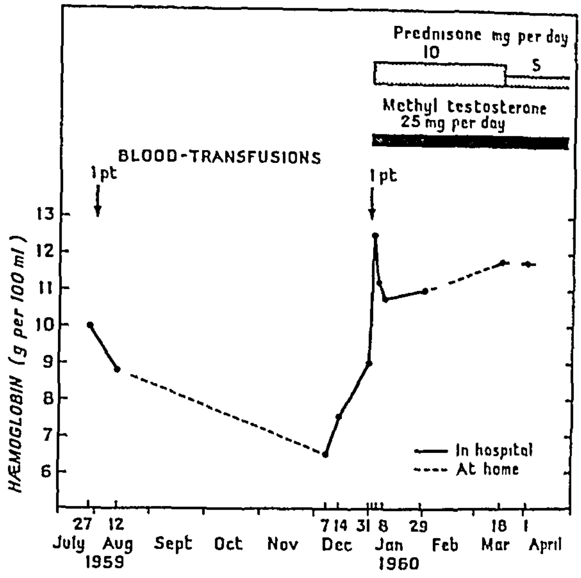

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Because of the Cushing effects the dose of prednisone has been reduced to 5 mg daily in each case and there has been some decrease in the children's weights In view of the genital overgrowth in the boy, it may be desirable to reduce the dose of methyl testosterone, but for the present it is being kept at the starting level

The results, especially in the girl, seem promising, but more than this cannot yet be claimed According to Shahidi and Diamond,[1] therapy will have to be continued for at least another 6 months, and it remains to be seen whether the improvement will thereafter be maintained without treatment It is not yet known whether further courses of the drugs are necessary or not This will depend on follow-up studies of peripheral blood and bone-marrow

The future may show that complete recovery is sometimes possible from this hitherto fatal disease

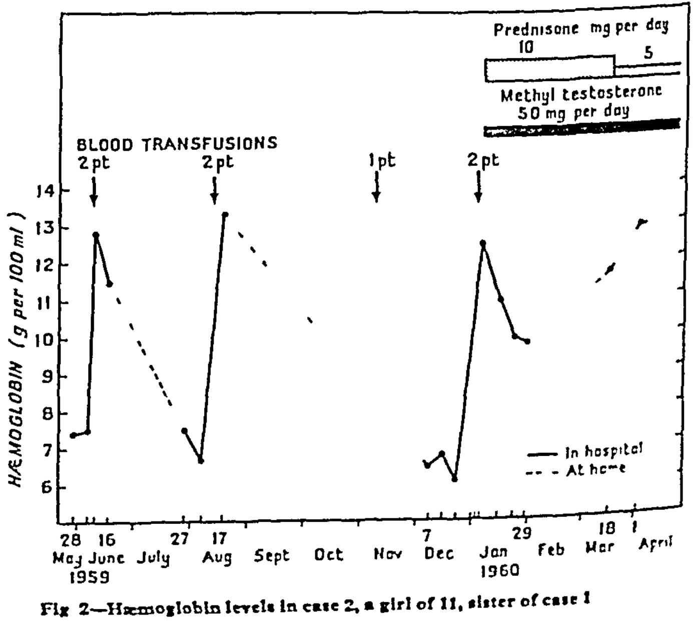

Fig 2—Hæmoglobin levels in case 2, a girl of 11, sister of case 1

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1 Shahidi N T Diamond L K *A.M.A J Dis Child* 1959 98 293
2 Diamond L K Personal communication, 1959
3 McDonald R Goldschmidt B L *Arch Dis Childh* (in the press)

Addendum—At the end of June, 1960, these children had been under treatment for 6 months, and in each case the hæmoglobin was over 13 g per 100 ml Bone-marrow activity was likewise satisfactory In view of the good response to treatment, both drugs have been reduced in amount, and it is intended to discontinue therapy in a month or two The blood-picture will thereafter be watched

Thanks are tendered to Prof. F J Ford for advice and Dr J G Burger, superintendent of Groote Schuur Hospital, for permission to publish this report, which is based on a paper presented to the 4th Congress of the South African Pædiatric Association in Cape Town on April 4, 1960

Department of Child Health
University of Cape Town, and
Groote Schuur Hospital,
Observatory, Cape Town.

ROBERT McDONALD

POSTPARTUM PRE-ECLAMPSIA

SIR,—May I congratulate Flight-Lieutenant McFadyen on observing and describing the phenomena recorded as "postpartum pre-eclampsia" in your issue of Nov 5? He will forgive me for pointing out that I did mention that such events do occur on pp 164 and 243 of my book, *The Pregnancy Toxæmias*, and for the first time in your columns in 1932[1]

Would it not be wiser to attribute all the "eclampsias" to disturbances in one or more of the homœostatic mechanisms rather than postulate a single cause for one or all of them?

Bradford.

G W THEOBALD

PERITONEAL SPLASH A PHYSICAL SIGN

SIR,—The letters by Mr Lane Roberts (Sept 24) and Mr Smiddy (Oct. 15) interested me, particularly because I have found it useful to try to elicit the presence of fluid in doubtful perforation

My custom in such doubtful cases is to auscultate the abdomen for bowel sounds, and the patient is asked to cough If there is fluid and air in the abdomen then a double sound is heard as the wave of fluid is displaced by contraction of the diaphragm The nearest English equivalent I can suggest is "tch-tch" When this is heard one can be confident that there is air and fluid in the abdomen, but it is not heard in every case, particularly in early perforation when there may be little fluid

Weymouth and District Hospital

J JEWERS

PULLED SHORT EXTENSORS

SIR,—I should like to describe briefly a new differential diagnosis of twisted ankle or foot—"pulled short extensors"

Since most patients have heard of twisted ankles many arrive in the casualty department with a history of having fallen and twisted their ankle. So severe is the initial pain that many arrive in the casualty consulting-room in a wheel-chair

The injury can happen at any age. In the cases I have reviewed the age-range is 11 to 64 years Nearly 25% of all foot and ankle injuries in the period May to December, 1959, were of this kind. *Clinical examination* shows considerable swelling over the dorsum of the foot near the origin of the extensor digitorum brevis No swelling of the ankle-joint is seen or palpable, and there is no tenderness over the styloid process of the 5th metatarsal bone. *Radiographic findings* are negative. One patient had ruptured short extensors associated with a fracture of the sustentaculum tali

A cold compress of lotio plumbi or saline is applied, and on the first day of the injury the patient rests at home. Seen in casualty again on the third day after injury, they have all recovered and are discharged—in contrast with the ankle sprain, which may require treatment for two weeks or more.

Bedford General Hospital

K A. TAYLOR.

SPONTANEOUS FRACTURE OF THE FIBULA

SIR,—Mr Maudsley (Nov 5) has, I think, oversimplified the explanation of "fatigue" fractures both in the fibula and in general

First, in the fibula, these fractures occur in infants, children, adolescents, young adults, and in middle age Secondly, I do not feel it is right to compare fatigue in living bone to fatigue that occurs in other materials, such as metal Undoubtedly a dead bone will suffer fatigue, but we have no good evidence that true fatigue occurs in normal healthy living bone

It is therefore presupposing the pathological changes to call these lesions fatigue fractures and it is wiser, in my opinion, to call them stress fractures

Stress Fracture Bureau,
Middlesex Hospital,
London, W 1

M B DEVAS

MODERN CLINICAL BIOCHEMISTRY

SIR,—Dr Osborn's letter (Nov 5) is the best argument that has yet been put forward for the establishment of independent biochemistry departments controlled by qualified scientists

His views are no more than we can expect from one who admits that he is prepared to put the clock back for more than a century, but what a pity it is that Virchow's attitude of 1855 should still dominate the minds of some pathologists Ehrlich was a great man, and amongst his numerous claims to fame stands the fact that he was the founder of chemotherapy, which is not the same as clinical biochemistry And what Tolstoy wrote in his *Tales* of 1903 is little to the point in a discussion on Modern Clinical Biochemistry If Dr Osborn would care to read something rather more recent, I would recommend the article in *Clinical Chemistry* last month by Prof J G Reinhold entitled The Professional Status of Clinical Chemists If he studies this excellent address, he may realise that there may be more than one side to a question

When Dr Osborn ranks the biochemist equally with the senior technician in the other subjects, he certainly does shock me, but he does not surprise me Many pathologists hold this view, but at least it is something of an improvement on Professor Cappell's description of biochemists as "other workers not medically qualified" and every little helps A little plain writing does a world of good, and Dr Osborn's contribution must have opened quite a few eyes Indeed, it is questionable whether he or I will do more on behalf of clinical biochemistry in its efforts to free itself from the pathological mentality of last century

In reply to Dr Pinkerton (Nov 5) I would say that if he, or anyone else, still believes that I have overstated the case, surely Dr Osborn's letter will convince him that the case has been severely *understated* Why should Dr Pinkerton think it "patently absurd" that each large hospital should have an independent biochemistry department? Many large hospitals in Edinburgh, Glasgow, and elsewhere have independent biochemistry departments and they maintain a high standard of work. Such departments have the great advantage that clinicians can approach the biochemist directly on any biochemical problem without the intervention of the pathologist, and vice versa It is a system which works with the minimum of trouble and might be copied elsewhere with considerable advantage

I have neither said nor implied that the biochemist should "go it alone" or work in a "watertight" department, and I know of no professional clinical biochemist who would support such an idea The modern clinical biochemist works in the closest cooperation with all clinical units by contributing his share of specialised work directly to the clinician in charge of the patient The clinician, *and the clinician alone*, is the one to decide on matters of diagnosis and treatment.

Dr Pinkerton's letter comes near to the suggestion that has often been made recently—that some new nomen-

clature is sadly needed It would appear that "Pathology" has at least three different meanings

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[1] *Lancet* 1932, ii 1380

(1) Pathology in the academic sense of morbid anatomy plus morbid histology which, whatever its failings as a definition, ensures that we know what we are talking about

(2) The pathology which not only includes the above, but which also has dominion over other, quite separate, subjects, such as biochemistry This may have been a good thing at the start of the century but it is hopelessly out of date today

(3) The pathology which claims to be the study of disease and to cover all aspects of ' medicine " as well as many of the sciences Such an omnibus definition would have no real meaning

A little clarification would save a good deal of ill-feeling But pathologists should beware of the term "integration" Far too often this mathematical term is apt to be confused with the expression "empire building" and does not inspire confidence

Department of Biochemistry,
Western Infirmary,
Glasgow, W 1

E B HENDRY

SIR,—May an obscure, humble, and wholly incompetent non-medical biochemist express grateful thanks to Dr Hendry (Oct 29) and Dr Woolf (Nov 12) for helping to banish the gloom induced by the Protocols of Professor Cappell (Oct 15) ? Indeed, Dr Woolf's comments are so identical with my own that I feel we must be in telepathic contact

I do not feel, however, that giving high-calibre scientists the privilege of ordering their own equipment or appointing their own staff (as enjoyed by, say, pharmacists or almoners) will attract them into the hospitals They will still have to contend with medically sycophantic nurses and administrators and will be either treated with contempt as irresponsible schoolboys or patronised as talented court jesters The stigma of being "non-medical" will never be eradicated, and it will be better for this country if its first-class brains are used in the cause of economic survival rather than frittered away on the trivialities of modern clinical biochemistry as practised in hospitals today

Swansea

E B LOVE

MYOCARDIAL INFARCTION DURING PREGNANCY AND PUERPERIUM

SIR,—We were very interested in the paper of Sept 3 by Dr Watson and his colleagues and should like to add an unusual case of our own

A 35-year-old Jewish Yemenite woman, 11 years in Israel, mother of 7 children, was admitted to our department in February, 1960, because of dyspnœa and cough She had been pregnant 12 times, aborted 3 times, and 2 of her children had died while in Yemen She had never been ill or suffered chest pain before Thirty days before admission she had given birth at term to a normal infant, there had been slight swelling of the feet during her pregnancy but otherwise it had been normal She had been well until the night before admission when she awoke with a feeling of oppression in the chest and breathlessness

We found an anxious, pale, and cyanosed woman with pulmonary œdema Her pulse was regular at 120 per min , a systolic murmur grade I–II was heard over the precordium, and the liver was enlarged 3 cm beneath the costal margin Her blood-pressure was 125/100 mm Hg, the erythrocyte-sedimentation rate was 75/110, the V D R L flocculation test was negative, total serum-cholesterol 292–312 mg per 100 ml , serum-proteins within normal range An X-ray of the chest confirmed the pulmonary œdema

The electrocardiogram on admission showed an incomplete left bundle-branch block E C G tracings during the following days showed that the left bundle-branch block had disappeared and been replaced by the pattern of anterior septal infarction deep Q waves in V_1, V_2, V_3 with dome-shaped ST segments and negative coronary T waves Further E C G tracings revealed the usual dynamics of myocardial infarction The patient was given digitalis and diuretics for the pulmonary œdema, but otherwise she recovered from her attack without specific treatment

She remained under our observation because of repeated precordial pains which gradually disappeared The laboratory findings returned to normal the blood-pressure fell to 100/70, the erythrocyte-sedimentation rate to 20/40, and the serum-cholesterol to 192 mg per 100 ml The liver diminished in size Further X-rays of the lungs and heart, barium meal, and intravenous pyelogram were normal She has since resumed her activities as a housewife

Not only is this one of the rare cases of myocardial infarction in the puerperium, but it is also rare to find myocardial infarction in a Yemenite woman During the past ten years we have seen in this department 1063 cases of myocardial infarction (835 men and 228 women), but never before in a woman in the puerperium or in a Yemenite woman before the menopause The incidence of myocardial infarction is generally very low [1-5] in Yemenite Jews, the disease being practically unknown among those Yemenites who came to Israel since 1949

Brunner et al and Toor et al [6] compared the serum-lipid levels of the different communities in Israel and found very low cholesterol levels in those who came to Israel from Yemen recently According to Toor et al the mean total serum-cholesterol for Yemenite women of the age of our patient (35–44) is 172 ± 26 mg per 100 ml It is significant then that our patient had a high serum-cholesterol level of 292–312 mg per 100 ml at the time of her attack, which fell to 192 after her recovery

All our attempts to find one of the unusual causes of myocardial infarction in this case were unsuccessful This was probably therefore an "atherogenic" occlusion of a coronary artery

Department of Internal Medicine A,
Rambam Government Hospital,
Haifa, Israel

HARRY BASSAN
JOSEPH K KAFTORI
YAAKOW KOGAN

CHRISTMAS GIFTS FUND APPEAL

SIR,—I should like to remind your readers who have not yet responded to the chairman's appeal that it is our custom to distribute the gifts some days before Christmas

I hope all who can will send their contributions marked "Christmas Gifts" to the Royal Medical Benevolent Fund, 37, St George's Road, Wimbledon, London, S W 19, as soon as possible

GEOFFREY H BATEMAN
Honorary Treasurer,
Royal Medical Benevolent Fund

LOOKING AFTER NURSES' CHILDREN

Dr N F COGHILL, *chairman of the West Middlesex Hospital medical committee, writes*

"Many hospitals short of nurses employ married nurses part-time and find them a great help Such nurses can more easily return to hospital work if their children are satisfactorily cared for during the day We have been thinking of starting a creche-cum-nursery-school at the West Middlesex Hospital, Isleworth, for the children of married trained nurses I would be most grateful to hear from anyone who has had experience of such a scheme and its difficulties "

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1 Dreyfuss, F *Amer Heart J* 1953 45 749
2 Brunner, D , Loebel, K., Fischer M Schick, G *Harefuah* 1955 49 1
3 Brunner D Loebel K *Lancet* 1957, i 1300
4 Brunner, D Loebel K *Ann intern Med* 1958 49 732
5 Brunner D , Manelis G , Loebl K *Lancet* 1959 i 1071
6 Toor, M , Katchalsky, A. Agmon J Allalouf D *ibid* 1957 i 1271

Parliament

Judicial Corporal Punishment

Because there seemed to be considerable support in the country and in Parliament for the reintroduction of corporal punishment as a judicial penalty, the Home Secretary at the beginning of this year asked his Advisory Council on the Treatment of Offenders to consider whether there were any grounds for doing so. Corporal punishment was abolished in 1948 and it was suggested that a review of the matter was desirable in the light of post-war trends in crime and of current opinion in the treatment of offenders. In their report,[1] published this week, the Council admit that at the outset of their inquiry some of their number felt that the reintroduction of this form of punishment might be justified as a means of checking the growth of crime in general and of hooliganism in particular. But after considering all the evidence put before them they had unanimously come to the conclusion that "corporal punishment should not be reintroduced as a judicial penalty in respect of any categories of offence or of offenders."

They found that there was a cleavage of opinion not only among the general public but also among people of knowledge and experience, whether the penalty should be reintroduced or not and also great divergence of views on such aspects of the problem as the offences for which it should be imposed and the groups of offenders to whom it should be administered. Though all admitted that it would be a retrograde step, the Council thought that it was not generally realised how retrogressive it would be. Corporal punishment was only abolished in 1948, but between 1861 and 1948 it was in fact only available for adults for robbery with violence. To reintroduce it, as some proposed, for all offences of violence against the person, in particular those committed by young hooligans, would mean "putting the clock back not twelve years but a hundred years."

The Council also point out that we are the only country which demands its reintroduction, and that to do so would damage our reputation as pioneers of enlightened methods of penal treatment. Nor do the Council believe that there is any assurance that its reintroduction would substantially reduce crime. They have found no evidence that it is an especially effective deterrent either to those who have received it or to others. Though, like many forms of drastic and severe punishment which have been abolished "as affronting the conscience of a civilised community", it would deter a few, the Council are not satisfied that the numbers would justify a form of punishment with so many disadvantages, which is not in tune with modern penal methods, and which would militate against the success of reformative treatment.

Many of the new methods introduced under the 1948 Act have not yet been fully tried and are likely to greatly develop in the future, when, for example, more detention centres have been opened. In the Council's view it is, therefore, too soon to conclude that these methods are inadequate. The Council also found that practical difficulties and objections, especially the inevitable delay between the commission of the offence and the infliction of the punishment, strengthen the case against judicial corporal punishment. Their conclusions will, they realise, be more readily accepted if alternative methods of checking crime are introduced, and, though it was not part of their task to suggest such measures, they mention that they were impressed by the arguments of many of their witnesses that the greatest deterrent is not fear of punishment but certainty of detection. This, they point out, can only be achieved by a fully staffed and efficient police force in all areas. They also noted a widespread feeling that the courts sometimes seemed to deal surprisingly leniently with offenders convicted, often not for the first time, of offences of violence. Though the Council realise that there may often be good reasons for this, they suggest that there are cases in which "a severe and exemplary punishment is often salutary." They consider that the courts already have adequate powers to meet this need. They end their report with the hope that their own recent recommendations for the treatment of young offenders[2] will be implemented before long. They are convinced that these and the methods contemplated by the 1948 Act are likely to prove "more effective in the long run than negative methods such as corporal punishment."

Finances of Scientific Societies

In the debate on scientific policy in the House of Lords on Nov. 9 Lord **Adrian** drew attention to an unexpected, and perhaps unintentional, difficulty which independent scientific societies may soon have to face. Because of a proposed change in the way they are rated, the help they get from the State may be reduced.

Progress in both pure and applied science, he believed, was immensely helped by all these independent bodies that had grown up, some to encourage particular branches of science, like the Chemical Society or the Geological Society, and some to encourage science in general, like the Royal Society and the British Association. They had been the main forum for the interchange of ideas. They had meetings and libraries. The Royal Society of Medicine, for instance, had the best medical library on this side of the Atlantic. They published their own journals, and they became the representative bodies that rewarded merit and could be called on for advice. They began, like most of our hospitals, supported entirely by voluntary contributions, but for more than a hundred years they had been assisted by the State in the provision of buildings for some of them, by exemption from rates and recently by grants for publications. It had been a thoroughly British arrangement. They had kept their freedom and independence, but the help they got from the State made it possible for them to shoulder the much greater responsibility they had to face nowadays when science grows overnight.

There was no serious complaint about the way the arrangement had been working recently, or about the good will of the Government toward the scientific societies, but they had lately become aware of a danger threatening their finances, and the finances of none of them were very large. Part of the aid which the State had given them had been in the form of exemption from rates, because the societies had come under the heading of a special kind of charity. But the system by which charities were rated was full of inconsistencies and needed to be tidied up. The Pritchard Committee had considered how to do the tidying up, and one of its proposals was that, in future, the societies which were now exempt ought to be made to pay half the full rateable value of their premises. (The scientific societies would not be the only sufferers, but Lord Adrian admitted that he was leaving the Arts to look after themselves.) If the scientific societies had to shoulder these new burdens without any increased help, they must put up their subscriptions and cut down their expenses—that is to say, cut down the journals they published and the meetings they arranged. If this change took place, no doubt the large national societies would survive. But some of the smaller bodies, which look after highly specialised branches of science, might be faced with extinction, and we might find ourselves paying too high a price for a tidy system of rating.

In the course of his reply to the debate Viscount **Hailsham** promised that he would look into the rating of the learned societies. The question was under consideration by the Government, but he was not sure what the answer would be. There were difficulties in the way of exemption from any tax. However, he saw the force of what Lord Adrian had said.

Public Health Bill

This Bill, which was published on Nov. 11, provides for the replacement of local building by-laws by regulations made by the Minister of Housing and Local Government and applicable throughout England and Wales outside the county of London. It would also amend the Public Health (Drainage of Trade Premises) Act, 1937, to enable local authorities to charge for the reception into the public-sewerage system of some trade effluents at present exempt, and it would classify as "trade effluents" farm effluents and effluents from premises used for scientific research It would empower the Minister to remove the exemption given to laundry effluents under the 1937 Act where their discharge would be likely to cause special difficulties in the treatment or disposal of sewage The Bill also incorporates into the general law some public-health provisions already included in local Acts These are for the most part modest extensions or adaptations of existing statutory provisions which the experience of local authorities has shown to be necessary, and deal with such matters as sewers and drains, water-supply, infectious diseases, streets, and parks and open spaces

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[1] Corporal Punishment. Cmnd. 1213. H.M. Stationery Office. 1960. Pp 58. 3s. 6d.

[2] Treatment of Young Offenders. H.M. Stationery Office. 1959.

QUESTION TIME

Foot-and-mouth Disease

Mr D G **Bullard** asked the Minister of Agriculture, Fisheries, and Food if he would make a statement about the present serious outbreak of foot-and-mouth disease —Mr **Christopher Soames** replied During the past eight days, 94 outbreaks of foot-and-mouth disease have occurred in parts of Eastern England and Scotland The most seriously affected areas are in Norfolk and Suffolk and in Northumberland, and wide movement restrictions have been imposed in East Anglia, Northumberland, Durham and in most of Scotland because infected cattle are known to have passed through markets in these areas My veterinary staff are doing their utmost to trace the origin of the outbreaks, but so far there is no clear indication of the cause

Doctors Overseas

Mr L A **Pavitt** asked the Minister of Health what consultations had taken place with the Colonial and Commonwealth Relations Offices to facilitate the acceptance by doctors of posts overseas and their subsequent reabsorption into medical service in the United Kingdom —Mr **Powell** replied I am not aware of any special obstacle to the reabsorption into medical service here of doctors who have taken posts overseas

Obituary

JOHN WALTER LENNOX SCOTT

C B , D S O , M R C S

Major-General John Scott, who died on Nov 6 at Crookham, was director of medical services in the British Expeditionary Force at the beginning of the late war After he retired from the Service he took charge of the large E M S hospital at Park Prewett

He was born in 1883 and was educated at Dulwich College and Westminster Hospital He qualified in 1905 and a year later joined the R A M C During the 1914–18 war he served in France and Belgium and was three times mentioned in despatches In 1918 he was awarded the D S O From 1926 to 1930 he was deputy assistant director-general at the War Office Later he became successively assistant director-general and deputy director-general of Army Medical Services He was advanced to the rank of major-general in 1937, and became D D M S , Eastern Command On his retirement in 1941 he was appointed C B

R E B , who as D D M S in Southern Command made arrangements with Scott for the reception of casualties at Park Prewett, writes

"Those were anxious days, with some 10,000 casualties arriving from the beaches in L S T s and other craft Later there were airborne evacuations and shiploads of invalid ex-prisoners of war from Japan and Germany During this period Park Prewett, the largest hospital in the command, was our great stand-by General Scott met the almost daily crises completely unperturbed, and the whole vast organisation worked with clockwork efficiency Never once did I appeal for his help in vain I never failed to receive his wholehearted support and kindly advice The part he played in these crucial years was a fitting end to a distinguished career"

General Scott leaves a widow and two sons

HENRY LEO BARNIVILLE

B A , M D , M Ch Dubl

Emeritus Professor Barniville, senior surgeon to the Mater Misericordiæ Hospital in Dublin, and a senator of the Irish Free State, died in Dublin on Sept 23, at the age of 73

From Rockwell College, Co Tipperary, he entered the medical school of the Old Catholic University in Cecilia Street He took his M B with first-class honours in 1911 in the National University of Ireland when University College, Dublin, was founded as a constituent college After spending a year as house-surgeon in the Mater Misericordiæ Hospital, he won the first medical travelling studentship offered by the new university With it he spent two years in Freiburg in Breisgau and a year in London in the Cancer Hospital in Fulham Road In 1915 he returned to Dublin as assistant surgeon to the Mater Hospital In 1918 at the age of thirty-two he succeeded to a vacancy on the senior staff In 1925 he succeeded to the chair of surgery at Dublin University College He was nominated to the first Senate of the Irish Free State, and he remained a member until the Senate was abolished in 1936 On its reconstruction in 1938 he was elected to represent the graduates of the National University and he continued to represent them In 1947 he sustained a detachment of the retina Though it was successfully operated on, he had to give up many of his outdoor pursuits and lead a life of restricted activity

A colleague writes

"Barniville's remarkable gifts and exceptional start in his professional career promised a future that was only partly fulfilled He never wrote anything and he never made a communication to the Academy of Medicine This is the more regrettable because he had accomplished much By the early forties he had over 500 cases of toxic goitre operated on with negligible mortality under the crude anæsthesia of that time The reasons for this omission are both simple and complex

"He reached success too early and by the age of thirty five was working so hard that he had scarcely the time for anything except work Dublin hospitals at that time were grossly understaffed with registrars and assistants, so that the drudgery of record-keeping and case-collecting had to be done personally by anyone who was preparing to write

"He was the kindest and most charitable of men, as many generations of students whom he helped could testify He was always a good and witty companion, and those who met him in his early years long cherished his memory He loved good company, a race meeting, a game of bridge, which he played with distinction, and the almost lost art of conversation In his professional work he had beautiful hands, a rare feeling for tissue, and imperturbable good humour which enabled him to ride out any storm His approach to the nervous or difficult patient was wonderfully reassuring, and when he had taken his patient's hand in his own and sat down beside the bed and spoken only a few words the relief of tension was immediate"

In 1910 Professor Barniville married Miss Brigid Weymes by whom he had three children, the youngest of whom is a doctor

HAROLD STUART BARBER

M D Dubl , F R C P I , M R C P

Dr Stuart Barber was one of the few physicians in this country who gave almost all his time to the care of patients with rheumatic diseases, and he played an important part in developing the rheumatology services in the Manchester region He died on Nov 8 at the age of 19

He qualified from Trinity College, Dublin, in 1933 and almost immediately joined the R A F medical branch He served as a medical specialist throughout the war but soon afterwards returned to civil life He held resident hospital appointments in London at the Prince of Wales' Hospital, Tottenham, and in the skin department at St Bartholomew's Hospital before settling in Buxton, where he succeeded Dr C W Buckley He was also assistant clinical director of the rheumatism research unit at the University of Manchester

In 1948, when the National Health Service was started, Barber was appointed consultant physician to Withington Hospital, Manchester, and the Devonshire Royal Hospital, Buxton He was a member of the Heberden Society and made many valuable contributions to clinical rheumatology, including papers on the psychogenic basis of some so-called rheumatic pains, the use and misuse of physiotherapy, and a myalgic syndrome His last paper, a report of an unusual form of familial osteodystrophy, appeared in our columns in June

Of his work in the region J H K writes

"At his hospitals Barber practised rheumatology as a specialty within medicine and was largely responsible for the conversion of the Devonshire Hospital, Buxton, from an outmoded spa hospital into a modern centre for the treatment of rheumatic diseases with an international reputation He faced his long illness with great courage and worked until two weeks ago He was a most courteous and thoughtful man who loved the Derbyshire countryside in which he lived and which his wife paints most effectively"

Public Health

Maternity Services in Glasgow

IN Glasgow last year less than 60% of parturient women were confined in hospital. In his annual report Dr W A. Horne, the city's medical officer of health, expresses disappointment that no progress was made during the year towards increasing this proportion, which, he says, should be not less than 75%, in order to secure the admission of all women who should be confined in hospital either for medical or for social reasons The regional hospital board has formulated plans for new maternity hospitals and for the provision of maternity beds in existing hospitals "Up to date not one additional bed has been provided, although some 90 beds are due to be available within a period of six months"

The perinatal mortality-rate for Glasgow was 45 5 per 1000 live and still births—a higher rate than that for any other city in Scotland or England.

Food-poisoning due to *Cl welchii*

Outbreaks of *Clostridium welchii* food-poisoning continue to be reported

In Edinburgh[1] 30 guests had diarrhœa and abdominal pain between eleven and eighteen hours after a wedding reception. Suspicion fell on steak pie, prepared on the previous day from 30 lb of stewing beef, which was all heated in a pot for an hour and a half, and then left with the lid off for eighteen hours in the kitchen On the morning of the wedding-day it was heated again for about three-quarters of an hour Four hours later—half an hour before the meal was served—the cook noticed that the meat smelt sour and had a peculiar taste He consulted the butcher, who, after stating that he had experience of cooking, put the meat in a colander and washed it under the tap Fresh gravy was made from gravy powder, and the meat was heated once more and served with pastry as steak pie. Heat-resistant *Cl welchii* was isolated from the stools of the patients

Another outbreak affected 77 pupils, 10 teachers, and 4 kitchen workers at a school. In this case mutton was to blame, it had been steamed on the day before consumption and left to stand overnight in a pantry

In 273 out of 723 cases of food-poisoning in Lancashire in 1959, *Cl welchii* was the causal organism[2]

At Dagenham[3] 98 children and 13 staff-members at a junior school were taken ill after eating lamb which had been cooked at another school The bacteria multiplied in the two hours before the meat was eaten.

The following measures[4] will help to avert this form of food-poisoning

Meat should be cooked so that heat-resistant spores are destroyed. Pressure-cooking is helpful, and joints should be thoroughly roasted.

If not eaten at once, the meat should be rapidly cooled and left in a refrigerator till required.

When meat is kept warm before being served, the temperature of the hotplate should be maintained at 60°C

Notification of Anthrax

From Dec 1 anthrax will be notifiable by medical practitioners to the medical officer of health of the district.[5] Cases of this disease in factory workers are already notifiable to the chief inspector of factories and in future such cases will also be notifiable to the medical officer of health

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[1] Annual report of the Public Health Department Edinburgh, for 1959

[2] Report of the medical officer of health for Lancashire for 1959

[3] The health of Dagenham in 1959 annual report of the medical officer of health.

[4] *Med Offr*, 1958, 99 340

[5] Public Health (Infectious Diseases) Amendment Regulations, 1960 *S.I. 1960 no 1959 H.M Stationery Office. 2d*

Appointments

CLARK, J R., M.B Edin. M.R.C.P.E. consultant physician, Borders hospital group

FRASER M. S, M.B. Edin. M.R.C.P.E consultant in medical pædiatrics, East Fife hospital group

MURPHY, LORETTA P, M.B N.U.I, D.P.H., D C.H. assistant M.O, Leicestershire

SPENCE A. J M.B Aberd. F.R.C.S. consultant orthopædic surgeon, East and West Fife hospital groups

The Hospital for Sick Children, Great Ormond Street, London

ECKSTEIN H B, M.D Cantab F.R C.S surgical registrar

FRY, H J H. M.B. Sydney, F.R.C.S house-surgeon orthopædic and plastic department.

GOODALL, JANET M.B Sheff, D OBST, D C.H. house-physician.

HARRIS, LEWIS M.B Glasg, D.P.M. resident registrar neurological and neurosurgical departments

SMITH, CLARE NEVILLE, M.B Cantab, D.P.H. assistant R.M.O, Tadworth.

South Western Regional Hospital Board

BRADFIELD, A M. M.B N.Z M.R C.P D.P.M. consultant psychiatrist South Somerset clinical area.

MCNULTY M R. M.B N U.I F.F.R., D.M.R.D consultant radiologist Bath clinical area.

MONTGOMERY J N M.D Belf M.R.C.P D C.H. consultant pædiatrician Plymouth clinical area.

Western Regional Hospital Board, Scotland

AITCHISON, J D M.B Glasg F.R.F.P.S M.R C.P consultant physician Stirling Royal Infirmary and associated hospitals

BARBER N K. M.B Leeds F.R.F.P.S consultant ophthalmologist Glasgow Eye Infirmary

BRODIE WILLIAM, M.B Glasg, F.R.F.P.S. assistant orthopædic surgeon, Glasgow Royal Infirmary

CAMERON J H M.B Glasg assistant ophthalmologist Ayrshire area.

CHERINGTON F J M.B Glasg assistant ophthalmologist Glasgow Ophthalmic Institution and Ayrshire area.

CHISHOLM, E. A. M.B Glasg, F.R.C.S.E. F.R.F.P.S. consultant orthopædic surgeon Dumfries and Galloway Royal Infirmary and associated hospitals

CRAWFORD, J M M.D Glasg M.R.C.O G D.P.H. consultant obstetrician and gynæcologist Falkirk and District Royal Infirmary and associated clinics

CUTHBERT RICHARD M.B Glasg D.M.R.D consultant radiologist Stirling and Falkirk areas

DEMPSTER W H., L.R.C.P.E D.M.R.D consultant radiologist Law Hospital Carluke

DYKES W S M.B Glasg F.F.A. R.C.S. D.A. consultant anæsthetist Western Infirmary Glasgow and associated hospitals

GIBB, MURIEL E M.B St. And. assistant E.N T surgeon, Glasgow Royal Infirmary

LAMB ROBERT M.D Glasg M.R.C.P.E. D.P.H. consultant in infectious diseases Renfrewshire area hospitals

MCGOVERN G P M.B Edin. M.R.C.P.E. assistant psychiatrist Stobhill General Hospital Glasgow

MORRISON A. M.B Edin assistant orthopædic surgeon Law Hospital Carluke

PASIECZNY T A. H M.D Warsaw assistant dermatologist and venereologist Glasgow Royal Infirmary, with duties at Glasgow venereal-disease clinics

ROBERTS, G B S M.D Glasg consultant pathologist Ayrshire area hospitals

SMITH MARY D M.D Glasg F.R.F.P.S M.R.C.P.E consultant pathologist (hæmatology) Stobhill General Hospital Glasgow

THOMSON W S T M.B Glasg consultant biochemist Southern General Hospital Glasgow

WILSON THOMAS M.B Glasg F.R.C.S.E. consultant ophthalmologist Glasgow Eye Infirmary

Notes and News

THE HOSPITAL "SERVICE"

In opening a three-day conference at Peebles on Nov 7, Lord Craigton, Minister of State for Scotland, asked how far the "hospital service" was in fact a service "It is all financed in one way, boards are appointed in the same way, members of each profession or grade of staff work on the same conditions and the same rates of remuneration In many ways the extremer variations in the standards of service for the patients that existed before 1948 have been removed And we have made some progress in reorganising and rationalising the pattern of the hospital and specialist services on the lines that were so widely advocated before 1948 ' On the other hand, there were still too many substantial differences in the scale of hospital provision, and a national service, paid for mainly out of taxation, could not normally justify such wide variations unless they were clearly necessary

Scotland, Lord Craigton pointed out, had five regional boards and over 80 boards of management all with the same duties and functions Yet there were remarkable differences in the way they approached their job—in the committee structure, in the frequency of meetings, in delegated authorities, and even in the kind of things on which members concentrated their attention "I find it hard to believe that *all* these differences are desirable and that everybody must be right *all* the time "

Again, every hospital board was an employing authority advertising and appointing to its own posts Hence the individual doctor, or nurse, or administrative officer, who was trying to obtain the right experience at the right time, faced career problems which he would not find in some of the other services, or even in some of the larger industrial undertakings In the long run it was in the interests of all the employing hospital authorities that a man or woman should be able to get this variety of experience, "but can the particular employer who is concerned only to fill a particular post take this wider view?"

Every hospital was different, but should they be quite so different as they were? By this time we ought to have formed a clearer idea of what should be the standard of good practice As soon as people got down to the detailed planning of new hospitals and new units within hospitals, questions began to be asked, to which there was no considered answer as to what should be the generally accepted standard "I am not suggesting for a moment that we can achieve or want a uniform standard or a uniform pattern that everybody must observe rigidly But it would be ridiculous and wasteful for every small group up and down the country to take each and every problem and work out their own solutions independently There ought to be some basic generally accepted doctrine which they can take as a starting-point and from which variations and adjustments can be made to suit their own particular circumstances "

In conclusion Lord Craigton said that, with the increasing complexity of modern treatment, people would have to work more and more as a team, as was now evident in highly specialised hospital units But this sense of membership of a team was spreading outside the hospital too, with growing emphasis on the outpatient department, peripheral clinics, domiciliary visits, and teamwork both with the family doctor and the other social services In fact, "the individual hospital as a focus of loyalties and traditions has proved to be no longer enough We are beginning to think more in terms of groups of hospitals serving communities and less in terms of what goes on inside the four walls of a particular building or cluster of buildings—of the services that the hospital provides rather than of the hospital itself "

He hoped that the hospital service would never be a service thought of in terms of discipline, uniformity and chains of command But we have perhaps something to learn from these services in terms of group loyalties and as regards the common outlook on strategy and tactics which when you come to analyse it is really an underlying agreement on what the main problems are and how they ought to be tackled "

WORLD HEALTH ORGANISATION

At a meeting in Geneva of the W H O Executive Board, which opened on Oct 25,[1] a working budget of $21,576,480 was recommended for 1962, of this, $110,033 was earmarked for health activities in the Congo The Republic of the Congo (Brazzaville) and the Republic of Mali were admitted to full membership of W H O

It was announced that the U S A would give $4 million to the malaria eradication special account in 1961 A resolution supporting the full use by 1963 of Russian as a working language of the Regional Office and Committee for Europe was adopted

APPOINTMENTS IN GENERAL PRACTICE

Appointment Systems in General Practice (35 mm and 16 mm, sound, black-and-white, 31 minutes, Great Britain, 1960) is the second of a series of films on general practice in a modern society to be produced for the *Medical World*

It consists of a photographic record of a discussion between a doctor who is using an appointment system in his urban practice, a family doctor with a country practice, and a woman representing the intelligent patient Dr Bruce Cardew is in the chair The advantages, operation, and administrative details of the scheme are described and debated, and a case is made for the adoption of appointment systems more widely in general practice

The film is probably intended to stimulate discussion, but family doctors who take the trouble to attend a meeting on the subject would like more information on the administration and costs This could be more suitably presented by the printed word with reproductions of typical appointment cards and a page from an appointments book showing how space is allowed for the unexpected patient

Copies of the film may be borrowed without charge from *Medical World*, 56, Russell Square, London, W C 1

A COT FOR THE ROOMING-IN OF NEWBORN BABIES

Dr J W Farquhar *writes from the Edinburgh University department of child life and health*

"The practice of accommodating the newborn baby beside his mother, and of making her largely responsible for his care, has made necessary the provision near her of clean napkins, baby gowns, cleaning materials, and such topical applications as dusting powder, oil, and cream These should be personal to the baby The mother's bedside locker can seldom take more than her own requirements, and the provision of an infant cotside locker, although effective, is expensive and space-occupying, and it increases the difficulty of floor cleaning

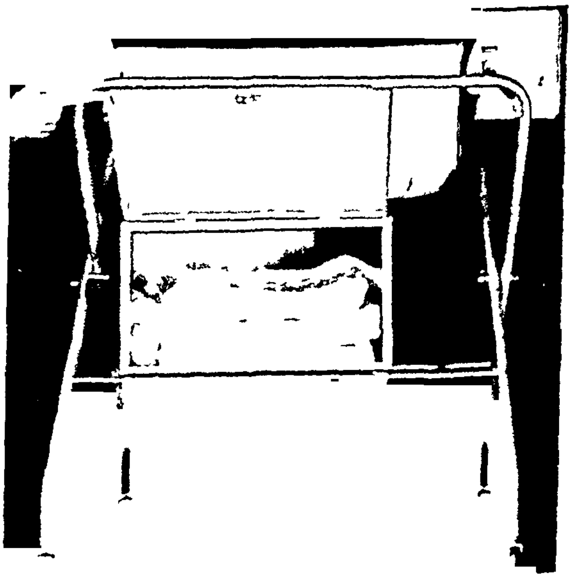

Fig 1

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[1] See *Lancet* Nov 5, 1960 p 1037 *ibid* Nov 12 p 1097

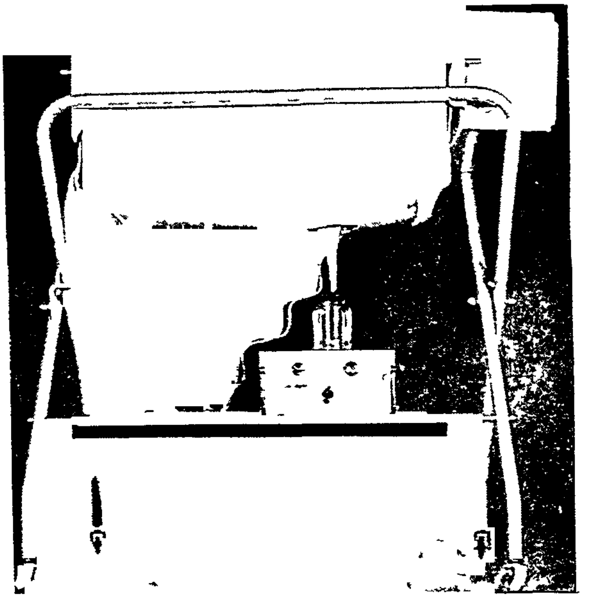

Fig 2

"The cot shown here (fig 1), which is an adaptation of that known as the Liverpool Maternity Hospital pattern, has been designed for this purpose at the Elsie Inglis Memorial Maternity Hospital, Edinburgh Strongly constructed and very stable, it has a tubular-steel folding frame mounted on well-running castors The canvas crib is suspended longitudinally, on removable steel rods, and it can be readily adjusted to give a slight declination at the head end It can be removed quickly, and is designed to facilitate laundering Although the crib is open slightly at each corner, the baby is perfectly warm, the body heat has not been lowered in fullterm infants nursed in them [1] The mattress, which is of latex foam, has a single faced hospital sheeting cover with zip fasteners

"A small locker, 13 in long, $5^1/_2$ in deep, and 7 in high, fitted to one end of the cot, has a closely fitting door, hinged at the top and held shut by a spring clip The locker is large enough to take the necessary cleaning materials and topical applications, and high enough to accommodate a plastic thermometer case holding an individual rectal thermometer in antiseptic solution The top of the locker has an identification-card holder A larger locker of 20-gauge sheet steel, measuring 18 in long, 10 in deep, and 10 in high, sits securely upon parallel steel rods below the canvas crib The door of this locker is also hinged above so that it will close by gravity, and it has a strong spring clip This locker provides adequate space for the day's supply of napkins, gowns, wraps, and blankets, and, at the Elsie Inglis Hospital where babies are weighed routinely on alternate days by spring balances, it also holds the personal knitted 'Terylene' mesh fabric net for suspension Both lockers can be easily lifted off the cot for cleaning

"The cot and all its fittings have a hard-baked enamel metallic finish, which is easily kept clean and which is resistant to antiseptic detergent cleaning agents The cot, with canvas crib, two lockers, and the mattress, costs about £15

"The cot is easily modified to collect urine from newborn babies A hole is cut in the latex foam mattress (fig 2) at a convenient point for male infants, latex tubing strapped over the penis passes through this hole to the collecting bottle on a tray beneath the crib, for females a 4-in polyethylene filter funnel is embedded in the mattress and its end passes through the canvas crib either delivering into a beaker or being connected to a collecting bottle by latex tubing The cot sheet has to be adapted for this purpose, and the hole is surrounded for some inches by light plastic sheeting which is folded into the funnel to prevent loss When the baby is positioned properly, the ankles are lightly tied to the corners of the cot with crepe bandage A single thickness of nylon stocking is placed over a brass ring in the mouth of the funnel to catch any meconium which may be passed An electrical alarm, which can be fitted to the funnel and accommodated on the tray, is so designed that the passage of a very small volume of urine will produce either urgent auditory or visual calls to the nursing staff in the room or at a remote station, they can then ensure that no urine is lost

"I am grateful to Messrs Spencer Mason, Ltd , for their cooperation, to Miss J Beckett, matron of the hospital, to Miss J Forrest, sister-in-charge of the newborn, and to Dr J M Kerr, medical superintendent of the Edinburgh Southern Hospitals Group, for helpful advice The filter-funnel technique of urine collection was modified slightly from that used at the Children s Medical Center, Boston, Mass, and the urine alarm unit was made for me by Mr Eric Leask of the department of medical physics, University of Edinburgh It will be described in detail elsewhere '

University of London

The title of professor of occupational health has been conferred on Dr R S F Schilling in respect of his post at the London School of Hygiene and Tropical Medicine

Dr Schilling, who is 49 years of age, was educated at Epsom College and St Thomas s Hospital After qualifying in 1934 he held house-appointments at St Thomas s In 1937 he became assistant medical officer at I C I (Metals) Ltd in Birmingham In 1939 he became a medical inspector of factories During the early part of the war he served with the R A M C In 1942 he was appointed secretary of the Industrial Health Research Board In 1946 he was awarded a Nuffield fellowship in industrial health, and then he joined the Nuffield department of occupational health in the University of Manchester, at first as lecturer, and later became reader His published work includes several papers on byssinosis in the cotton industry, and in 1956 he gave the Milroy lectures to the Royal College of Physicians of London, choosing as his subject chronic respiratory disease among cotton and other textile workers In the same year he was appointed to his present post He is a past president of the Association of Industrial Medical Officers He has also served as editor of the *British Journal of Industrial Medicine*

University of Sheffield

A course in dermatology for general practitioners will be held from March 20 to 24 at Sheffield Royal Infirmary Further details will be found in our advertisement columns

Royal College of Surgeons of England

At a meeting of the council on Nov 10 with Sir Arthur Porritt, the president, in the chair, Dr W E Lloyd was admitted to the board of examiners for the fellowship in the Faculty of Anæsthetists Arrangements were made whereby the professorship of military surgery at the Royal Army Medical College should become a joint professorship with the Royal College of Surgeons

Licences to practise and a postgraduate diploma were conferred on those named in the report of the comitia of the Royal College of Physicians in our issue of Nov 5 (p 1039)

Royal College of Physicians of Ireland

At recent examinations the following were successful

M R C.P I—P J Faul G A Kernohan
D Obst—T F Canty M Ahmad Genaidy

Royal Society

One of the Royal medals of this society has been awarded this year to Sir Roy Cameron for his work on cellular pathology

Chadwick Trust

On Thursday, Nov 24, at 5 P M , at 90, Buckingham Palace Road, London, S W 1, Dr R Scott Russell, head of the radiological laboratory of the Agricultural Research Council, will give a Malcolm Morris lecture His subject will be radioactivity in human diet

Royal Society of Medicine

The Blair Bell medal for 1960 has been awarded to Prof F J Browne, of Sydney On Oct 28, at a meeting of the section of obstetrics and gynæcology, his son, Prof McClure Browne, received it on his behalf

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[1] Farquhar J W Ratcliffe S Report of the Elsie Inglis Memorial Maternity Hospital for 1959

Charing Cross Hospital Medical School

On Thursday, Nov 24, at 5 30 P M, after the opening of the new surgical unit at the hospital, Prof A J Harding Rains will give his inaugural lecture at the Royal Commonwealth Society, Craven Street, London, W C 2 The title of the lecture will be A Chapter of Accidents

Problems of Youth

The National Council for the Unmarried Mother and her Child will hold a discussion on this subject on Thursday, Jan 26, at 5 P M, at County Hall, Westminster Bridge, London, S E 1 The chairman will be Dr David Stafford-Clark

Research Defence Society

On Tuesday, Dec 6, at 5 30 P M, at University College, Gower Street, London, W C 1, Prof J H Burn will give a Stephen Paget lecture His subject will be Testing Drugs on Man

International Embryological Conference

This conference will be held at the Middlesex Hospital Medical School, London, W 1, from Sept 18 to 21 Particulars may be had, after May 1, from Dr L Brent, department of zoology, University College, Gower Street, London, W C 1

Road to Maturity

On Thursday, Jan 26, at 10 30 A M, the Central Council for Health Education will hold a conference on this subject Further particulars may be had from the medical director of the council, Tavistock House, London, W C 1

Fulbright Travel Grants

Travel grants will again be available to citizens of the United Kingdom to go to the United States of America for academic or educational purposes Full particulars may be had from the United States Educational Commission in the United Kingdom, *71, South Audley Street, London, W 1*

McGibbon Lectures

Dr A Rae Gilchrist will give the inaugural lecture of this series, instituted by the Scottish Radiological Society in memory of the late Dr John P McGibbon, on Saturday, Feb 18, at 2 30 P M at the Royal College of Physicians of Edinburgh He is to speak on radiological contributions to cardiology

Molecular Basis of Neoplasia

This subject has been chosen as the theme of the 1961 symposium on fundamental cancer research which is to be held from Feb 23 to 25 by the University of Texas M D Anderson Hospital and Tumor Institute Further particulars may be had from the publications department, Texas Medical Center, Houston 25, Texas

Stroke Rehabilitation

The Chest and Heart Association is to hold a conference on this subject on Friday, Dec 9, at 2 P M, at B M A House, Tavistock Square, London, W C 1 The speakers will include Prof C B Perry, Dr John Marshall, Dr T H Howell, Dr Denis Leigh, and Dr Frank Cooksey Further particulars may be had from the Associaton, Tavistock House North, Tavistock Square, W C 1

On Wednesday, Nov 23, at 5 15 P M, at the Royal Free Hospital, Gray s Inn Road, London, W C 1, Dr M M Suzman of Johannesburg will give a lecture on long term use of anticoagulants

On Friday, Dec 2, at 8 30 P M, at Whipps Cross Hospital, London, E 11, Superintendent G E Salter of New Scotland Yard will give a lecture on counter-criminal methods

Sir Benjamin Rycroft is to be a guest speaker at an eye surgery clinical meeting which is to be held at the department of ophthalmology in the University of Toronto from March 20 to 22

Heinz fellowships of the British Pædiatric Association have been awarded to Dr H B Wong (Singapore), Dr G H Holman (Saskatoon), and Dr C A Reindorf (Toronto)

Diary of the Week

NOV 20 TO 26

Monday, 21st

UNIVERSITY OF LONDON
5 30 P M (London School of Hygiene and Tropical Medicine Keppel Street, W C 1) Prof C L Lumsden Pathology and Pathogenesis of Multiple Sclerosis

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road W 12
1 P M Dr Brian Ackner Hysteria

HUNTERIAN SOCIETY
8 30 P M (Apothecaries Hall, Black Friars Lane, E C 4) Canon C E Raven, Mr R S Murley (for), Mr I L Marks Dr Fred Wrigley (against) That Advertising Does More Harm Than Good

Tuesday, 22nd

BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Dr D A G Galton Contributions of Chemotherapy to the Study of Leukæmia

INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr C D Calnan Effects of Chemical Agents, Primary Irritants and Sensitisers

ST MARY'S HOSPITAL MEDICAL SCHOOL W 2
5 P M (Wright-Fleming Institute) Prof Frank Goldby Relation of the Nervous System to the Female Pelvic Organs

ROYAL ARMY MEDICAL COLLEGE, Millbank, S W 1
5 P M Prof A G R Lowdon Treatment of Acute Vascular Insufficiency In the Limbs

MANCHESTER MEDICAL SOCIETY
4 30 P M (Medical School, University of Manchester) Mr A R Anscombe Deaths of Three American Presidents

LEEDS NEUROLOGICAL SCIENCES COLLOQUIM
5 15 P M (General Infirmary at Leeds) Mr John Hankinson Surgical Treatment of Parkinsonism

ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Nicolson Street, Edinburgh
5 P M Dr Kristian Kristiansen (Oslo) Selective Cooling of Organs with Special Reference to the Brain

Wednesday, 23rd

ROYAL SOCIETY OF MEDICINE 1, Wimpole Street, W 1
8 30 P M *Proctology* Mr R W Nevin Review of Granulomata of Large Intestine (Presidential address)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Dr Victor Wynn Acid base Metabolism

INSTITUTE OF DERMATOLOGY
5 30 P M Dr J O Oliver *Hæmopoietic System in Skin Diseases*

INSTITUTE OF DISEASES OF THE CHEST Brompton S W 3
5 P M Mr T Holmes Sellors Diaphragmatic Hernia

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE 28, Portland Place W 1
3 30 P M Dr Hugh Gough Thomas Research in the School Health Service

WEST LONDON MEDICO CHIRURGICAL SOCIETY, West London Hospital W 6
8 30 P M Prof A J H Rains, Dr Hugh Jolly, Miss Helen Mayer Recent Advances in Treatment

UNIVERSITY OF OXFORD
5 P M (Radcliffe Infirmary) Prof J T Ingram Clinical Significance of the Minute Vessels of the Skin (Litchfield lecture)

UNIVERSITY OF LEEDS
5 P M (General Infirmary at Leeds) Sir Andrew Claye Forceps Today
6 P M Miss U M Lister Biochemical Changes in Pregnancy

Thursday, 24th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln s Inn Fields, W C 2
5 P M Mr J F Nunn Distribution of Inspired Gas During Thoracic Surgery (Hunterian lecture)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Dr H B Hewitt Fundamental Aspects of the Radiotherapy of Cancer

INSTITUTE OF DERMATOLOGY
5 30 P M Dr Calnan Cutaneous Allergy (First of two lectures)

INSTITUTE OF LARYNGOLOGY AND OTOLOGY 330, Gray s Inn Road W C 1
5 30 P M Dr E H Mercer Fine Structure of the Normal and Malignant Cell

LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8 15 P M (11 Chandos Street W 1) Dr M N Pai Role of Hypnosis in Treatment

CIBA FOUNDATION LECTURE
5 P M (Medical School Edgbaston Birmingham) Dr P J Thung (Amsterdam) Ageing in the Gonad Adrenal System

HONYMAN GILLESPIE LECTURE
5 P M (University New Buildings Teviot Place Edinburgh) Sir Stanford Cade Synovial Sarcoma

UNIVERSITY OF ST ANDREWS
5 P M (Physiology Department, Queen s College Dundee) Prof J I Malcolm Pharmacological Dissection of the Central Nervous System

Friday, 25th

ROYAL SOCIETY OF MEDICINE
4 30 P M *Pædiatrics* Mr W J W Sharrard Dr C O Carter, Mr J A Wilkinson Mr L W Somerville Infantile Hip Disease

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A M Mr Ian Fraser Problems in Pædiatric Surgery
4 P M Prof A Querido (Leiden) Goitrous Hypothyroidism
5 30 P M Prof W W Mushin Controlled Respiration

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
4 30 P M Mr Francis McGuckin Aetiology of Chronic Otitis [illegible]

BRITISH TUBERCULOSIS ASSOCIATION
5 P M (Joint meeting with the British Association of All[illegible] 26 Portland Place W 1) Dr J D [illegible]erall Dr J [illegible] Smith Dr S Z [illegible] Dr N W Horne Hypersensitivity Reactions to Antituberculous Drugs

BRITISH SOCIETY FOR IMMUNOLOGY
9 30 A M (183 Euston Road N W 1) Opening of two day symposium on Stimulation of Antibody Production

The Lancet · Saturday 26 November 1960

DISEASES OF THE BASAL GANGLIA

THEIR RELATION TO DISORDERS OF MOVEMENT

D. Denny-Brown
O.B.E., M.D. N.Z., D.Phil. Oxon., LL.D. (hon.), F.R.C.P.
PUTNAM PROFESSOR OF NEUROLOGY,
HARVARD MEDICAL SCHOOL, BOSTON, MASS.

(Concluded from p. 1105)

II

Before proceeding to physiological analysis it is necessary to define some of the terms employed and to indicate some general relationships.

One of the most prominent features of diseases of the basal ganglia is *athetosis*. The use of this term is based on its literal meaning of instability of posture, which, in the hand, implies various degrees of swing from a hyperextension of the fingers and thumb, often with pronation of the wrist, to full flexion of fingers (usually trapping the previously flexed thumb), with flexion and usually supination of the wrist. The swings of movement may be only partial when the condition is mild in degree. The hand is almost always involved, the lips, jaw, and tongue more particularly in bilateral cases, and the foot least prominently.

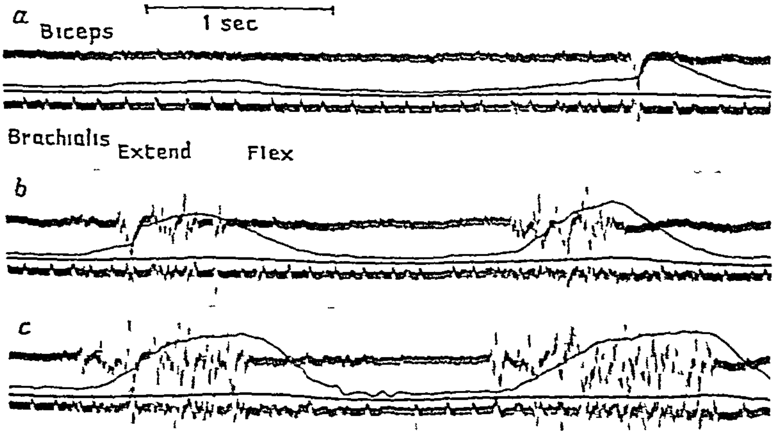

Fig. 8—E.M.G.s of biceps and brachialis anticus, both flexors of elbow, in a patient with paralysis agitans who has been relaxed until rigidity lessened.

In *a* gentle alternating flexion-extension of elbow through about 5° is passively performed. The alternating passive movement is gradually increased in amplitude with each repetition.

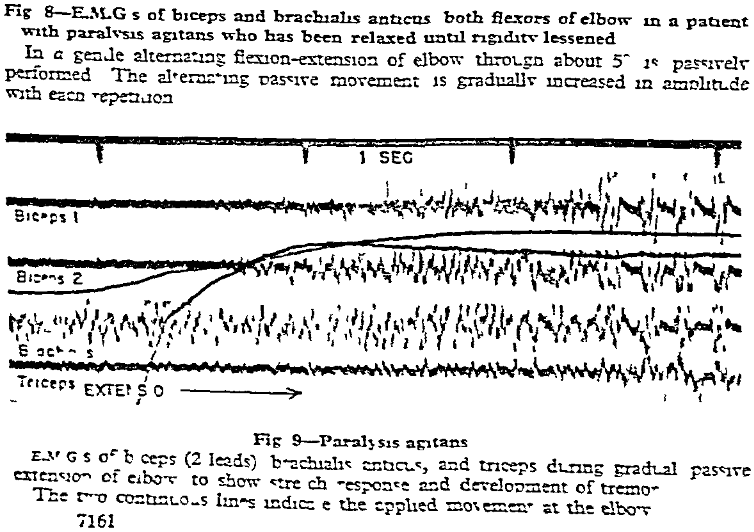

Fig. 9—Paralysis agitans.

E.M.G.s of biceps (2 leads), brachialis anticus, and triceps during gradual passive extension of elbow to show stretch response and development of tremor. The two continuous lines indicate the applied movement at the elbow.

Chorea is a word with many meanings. In the present connection it relates to a continued endless series of movements of the hand and wrist, of the lips, face, and tongue, and of the distal parts of the lower limbs. In their most subtle form the movements are automatic and conflicting reactions to environmental stimuli of all kinds. In more coarse form they become the movements of athetosis, but in choreic movement there is a continual flow of motion without the irregular alternation that characterises athetosis. In choreic movement posture is lost, in athetosis two or more habitual postures can be distinguished.

Rigidity is the common manifestation of parkinsonism. It is essentially a resistance to passively applied motion, distinguished by its plastic quality, presenting a relatively constant resistance throughout the whole range of applied movement. Rigidity is first appreciable in the flexors of wrist and fingers, but as it develops it is felt in both flexors and extensors of both limbs. In most cases of parkinsonism it is a little more prominent in all flexor muscles. Its presence in the face, tongue, and palate can only be inferred from the impedence of small movements in these parts. It is commonly stated that the tendon reflexes are not altered. They are certainly not increased in amplitude in proportion to the degree of resistance to stretch, as they are in spasticity. Electromyographic (E.M.G.) recording shows that a large tendon reflex is present as an electrical response fluctuating in amplitude according to the phase of tremor in which the tendon tap falls.

As shown previously (Denny-Brown et al. 1953) the plastic rigidity of parkinsonism and its action potentials can be made to disappear if the limb is completely supported, and the patient instructed to relax. Such complete inactivity is easily obtained in arteriosclerotic parkinsonism, less easily in paralysis agitans, and with most difficulty, though occasionally, in postencephalitic parkinsonism. Once the muscles relax completely, with corresponding electrical silence in flexors and extensors, then unimpeded passive movement is possible in either direction at any joint within a small range of 5–10° (the “ free interval ”). Movement of larger range immediately sets up a contraction in the stretched muscle, whether flexor or extensor (fig. 8), demonstrating that the rigidity is a stretch reflex in each muscle concerned. The “ cog-wheel ” phenomenon is due to the presence of tremor rhythm, leading to steps of relaxation in the resistance to passive movement. Though common, it is not an essential feature.

The plastic quality of parkinsonian rigidity that distinguishes it from spasticity, is due to a tendency of motor units recruited into a contraction by stretching, to drop out again one by one as others are recruited. The total number of motor units discharging as the muscle continues to be stretched, and the corresponding contraction, therefore tend to remain relatively small, giving the plastic quality When a spastic muscle is stretched more and more motor units respond, and resistance to stretch mounts to a peak At this point many units suddenly cease responding, and resistance to further stretch melts away (" lengthening reaction ") In plastic rigidity the lengthening reaction affects one motor unit after another from the beginning of stretch, so that resistance to stretch remains approximately constant

If tremor also complicates the rigidity the appearance and disappearance of units during steadily increasing stretch (after preliminary relaxation) gradually synchronise, until eventually at one point they all cease discharge together and return together This is the first beat of tremor, and there is commonly a concurrent burst of units in other related muscles at the same joint (fig 9), then in other previously quiescent muscles in the limb

Dystonia is a term that has also been used in many senses I would define it as a fixed or relatively fixed attitude, in association with some other extrapyramidal disorder of movement In its mildest form it is seen as overextension of the fingers with slight pronation, or as fixity of facial expression (most commonly openmouthed with staring eyes), or continued overinversion of a foot In greater degree the extremity becomes set in one of the postures of athetosis, with eventual distortion of the lips and tongue, torticollis, or tortipelvis The muscles concerned in the fixed posture offer an increasing resistance the more the part is moved away from its primary position In intense dystonia the resistance to attempted passive movement is springy in quality, and the part flies back to its habitual posture when released In less degree dystonia presents a plastic rigidity with perhaps very slight palpable increase in resistance as the limb is moved away from the dystonic posture The E M G is indistinguishable from that of parkinsonian rigidity As dystonia becomes more intense, more and more of the motor units fail to show a lengthening reaction, and they continue to discharge as still more units join the response Contractile resistance then steadily increases with increasing stretch

In the dystonias of postencephalitic parkinsonism and of dystonia musculorum deformans different parts of the body are separately involved The resulting postures are usually asymmetrical and incongruous I shall refer to this type as *segmental dystonia*

The mode of onset of abnormal attitudes in Wilson's disease is usually different Both limbs on one side are affected together Very gradually slight abnormalities of attitude become more fixed, and the abnormal attitude develops as a whole It is then seen, as so well described by Wilson (1912), as flexion of both upper limbs, with hyperflexed, slightly pronated wrists, and at first overextended and later overflexed fingers The lower limbs are extended, and the ankle-joints plantar-flexed and inverted This condition is usually referred to as the rigidity of Wilson's disease, but by my definition it is dystonia In the early stages it is a plastic rigidity, but gradually the lengthening reaction is lost I call it *hemiplegic dystonia* from its general resemblance to the pattern of hemiplegic spasticity, and from its tendency to affect all the parts on one side together

Finally one must recognise that, particularly as an end stage in paralysis agitans and related states, a persistent attitude of flexion may occur in all limbs—the wrists over-flexed and pronated, the fingers extended, the lower limbs flexed on the abdomen, and the feet stiffly plantar-flexed In this condition the abnormal attitude tends to develop as a whole In milder degrees it also has a background of plastic rigidity, with steady neuronal discharge in proportion to the degree of maintenance of the abnormal attitude I shall refer to it as *generalised flexion dystonia* It is the pallidal syndrome

Tremor—By common usage tremor is a rhythmical alternation in movement at a rate of more than one beat a second It must be recognised, however, that the disorder may begin with isolated single beats, as in " liver flap" The relation of tremor to movement is only of relative value in distinguishing types of tremor Whereas parkinsonian tremor is first apparent only in very slight degrees of muscular contraction, as the tremor becomes more intense it is apparent during greater degrees of contraction and in full development may never be absent

The term *myoclonus* has many different connotations It is essentially an unpredictable rapid jerk or twitch of one or more muscle groups, distinguished from chorea by its abruptness and brevity Any muscle group may be involved, but an abrupt flexion of one or more joints in both upper limbs, with extension of the neck, are frequent components The jerks may at times appear in a rapid series of two or more in succession Myoclonus of this type is common in extrapyramidal disease We must omit from this brief account its relation to " palatal " myoclonus, epileptic myoclonus, and other types of bulbar and spinal twitching of similar kind

Interrelations of the Motor Disorders

Chorea, Athetosis, and Parkinsonian Tremor

Although it is a diagnostic convenience to separate these various types of motor disorder, the first step in gaining a proper understanding of their significance is to seek relationships between them The model for this whole series seems to me to be the phenomenon of athetosis If one has in mind the two elementary postures of the fingers and wrist—overextension with pronation and overflexion with supination—between which the movement alternates, one may find the same two postures in post-hemiplegic athetosis and in double athetosis, though the speed of alternation is faster in the latter The involuntary movements of Huntington's chorea reproduce momentarily the same postures again and again, with many partial variants (Denny-Brown 1950), gradually becoming more stereotyped In dystonia musculorum deformans one or other posture is found as a fixed attitude (Denny-Brown 1945) In the rapidly progressive type of Wilson's disease the transition from choreic movement to athetosis to dystonic attitude may be observed in the same patient in the course of months Most commonly the dystonic fixation of the hand in Wilson's disease is with fingers extended, though in time the wrist becomes overflexed (fig 2) Very rarely a dystonic attitude of overflexion of the fingers is present from the beginning, and the hand ultimately develops a severe dystonic grasp which the patient is unable to relax

In some unusual variants of Wilson's disease dystonia develops only very slowly, and in such cases a parkinsonian tremor may eventually supervene after months of athetosis When this happens the athetosis gradually becomes more rapid, and the amplitude of movement less The fingers, instead of closing over the previously overflexed overadducted thumb, now close only to semiflexion —the adducted thumb also—and at more rapid intervals Eventually the partial movement, more regularly repeated, becomes the "pill rolling ' tremor of parkinsonism,

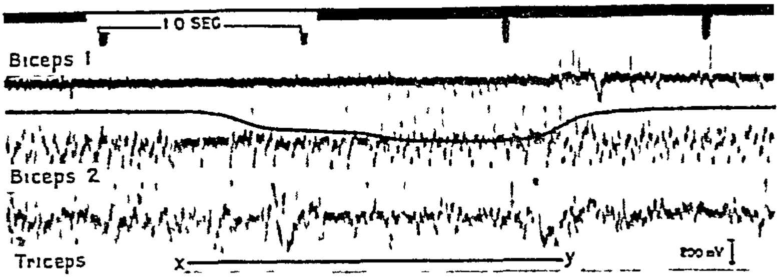

Fig 10—Arteriosclerotic parkinsonism

E.M.G s of biceps (1 and 2) and triceps during flexion (x) and extension (y) of elbow

with appropriate opposition of the thumb (Denny-Brown 1950)

Chorea, athetosis, and parkinsonian tremor are also topographically related, for each involves primarily the hand, in next degree the lips and tongue, and in ultimate development the ankles We therefore regard them as members of a related series of fluctuations of posture with important physiological connotation

Parkinsonian Rigidity, Dystonia, and Myoclonus

In the more intense plastic rigidity of parkinsonism, particularly in arteriosclerotic types with little tremor, the lengthening and shortening reactions at first become more fully developed When the elbow is extended there is a burst of discharge in the flexors followed by relaxation to the previous level The phase of relaxation (lengthening reaction) occurs earlier than in stretch of a spastic muscle, and coincident with it is a contraction in the extensors (shortening reaction) (fig 10) On flexing the elbow the reverse process readjusts the quantity of contraction to its previous level Both flexors and extensors show a rapidly adjusting stretch reaction Later, as dystonia becomes more pronounced, fewer of the motor units exhibit a lengthening reaction in the flexor group in the upper limb, and they continue to discharge as long as stretch is maintained The extensor group then show correspondingly less shortening reaction Ultimately, when dystonia is fully developed, all the discharge is directly proportional to length of muscle, and the lengthening and shortening reactions have vanished. This progressive loss of lengthening reaction in the elbow flexors is associated with two other features—(1) the activation of other synergic flexors by stretch of one of them, and (2) increasing numbers of units continuing to discharge at the shortest length of the muscle Some of these are stimulated by tension on other flexor muscles and they can be got to cease discharge by more complete relaxation Some are influenced by labyrinth and neck reflexes and can be silenced only by manipulating the head and neck

At an intermediate stage of development of dystonia of hemiplegic distribution, when many units still show lengthening and shortening reactions, a rapid stretch provokes discharge of a large number of motor units together, dissipating in several beats, during one or more of which bursts in widespread synergist muscles cause the sudden contraction that the clinician calls a "myoclonic jerk"

These observations, which can readily be repeated while any type of dystonia is developing, indicate that the essential conflict between proprioceptive inhibition and excitation in all these types of rigidity and dystonia is one of degree and not of kind

Tremor and Rigidity

As already mentioned, in dystonic states the lengthening reaction in one muscle is associated with a shortening reaction in its antagonist If the plantar flexor of the foot, or palmar flexor of the wrist, is suddenly stretched, the response in the shortened antagonistic extensors is often visible to the eye as a brief contraction of the tendons of corresponding pretibial or wrist dorsiflexors Fig 11*a* is an E M G record of this phenomenon, which is generally known as "Westphal's paradoxical reaction" (Westphal 1878), or as the "tonic postural reflex" of the French school (Foix and Thevenard 1923) Like Kinnier Wilson (1925) and others, I have found the sign to be inconstant in paralysis agitans and Wilson's disease, though it is prominent in some cases A corresponding delayed burst of discharge in the wrist extensors follows 60–70 msec after a tendon reflex in the finger flexors under these circumstances (fig 11*b*) Matthews and Rushworth (1957) found that procaine infiltration of the motor point of a muscle selectively paralysed the gamma efferents to the muscle spindles Two years ago, with Dr Geoffrey Rushworth I reinvestigated this phenomenon and found that such infiltration of the motor point of a dystonic muscle, whether wrist flexor or post-tibial muscles, abolished the reaction to stretch both in the muscle concerned and in its antagonist, leaving it still possible to innervate either group by will The reaction is therefore clearly proprioceptive, and it is related to the antagonistic autogenetic reflex excitatory effect of the annulospinal endings versus the inhibitory secondary sensory flower-spray endings of the muscle spindles

This double effect demonstrates clearly that such plastic states represent the release of two opposing types of stretch reflex The prominence of the paradoxical reaction in wrist and ankle is related to an intermediate phase of development of dystonia in these groups, so that the sudden stretch falls on muscles that are already contracting With a lesser degree of dystonia there is no reaction, and in greater dystonia all the response is in the stretched muscle

When tremor complicates moderate dystonia the first response of the stretched muscle is a prolonged beat of

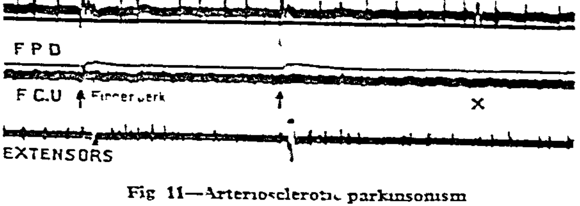

Fig 11—Arteriosclerotic parkinsonism

E M G s of flexor profundus digitorum (F P D), flexor carpi ulnaris (F C U), and extensors of wrist, during sudden passive dorsiflexion of wrist (*a*), and during finger jerks (*b*) X represents a subliminal tap on the finger flexors tremor, the cessation of which is associated with a similar prolonged beat of tremor in the antagonist Tremor then appears as a series of alternating primary and paradoxical reactions A final prolonged burst of tremor when a tremulous muscle is suddenly shortened is the reverse reaction From this point of view tremor is a rhythmical alternation of the conflict of the same heightened proprioceptive reciprocal effects that are represented in the lengthening and shortening reactions of dystonia

The observation of Walshe (1929) that parkinsonian rigidity could be abolished by cocainisation of the motor points of a rigid muscle, leaving tremor unaffected, might appear to contradict these conclusions The explanation lies in the spread of contraction, whether rigidity or tremor, from one muscle to another The stretch reflex can no longer be elicited in a cocainised muscle, but the paradoxical reaction or tremor from other muscles can still affect it Total surgical deafferentation of the limb by dorsal-root section, reported by Pollock and Davis (1930), also demonstrates the point, for then only a variable degree of slowly rhythmical neck and labyrinthine reflex remained

These findings indicate that plastic rigidity, parkinsonian tremor, and dystonia are different aspects of a conflict of released proprioceptive reactions The conflict is resolved more slowly in plastic rigidity, more rapidly and rhythmically in tremor, and not at all in intense dystonia To find the reason for these conflicting aspects of release of low-level reflexes we must turn to the question of cortical control of proprioceptive reactions

The Two Basic Postures of Athetosis

In earlier studies of disorders of movement produced by cortical lesions (Denny-Brown 1958), I have distinguished two general types of disorder

The first type is represented by the tendency of medial frontal-lobe lesions to facilitate tactile and visually directed palpatory reactions in the hand and lips, of which the instinctive grasping and sucking reactions are the prototypes The fundamental change in behaviour is more general and comprises all the manifold elements of frontal apraxia, including a stiffening of the whole limb in response to contact (gegenhalten)

The second type is an opposing set of reactions, released by parietal-lobe lesions, characterised by instinctive tactile and visual avoiding responses which determine withdrawal, flexion of the limbs, over-extension of the fingers, and residual stiffening of the limb in this posture ("catatonic persistance of attitude") Two general areas of cortex, medial frontal and lateral parietal, are organised in this respect, with corresponding visual exploratory and avoiding responses in the posterior-parietal and temporal regions (Denny-Brown 1956, Denny-Brown and Chambers 1958)

These two physiological types of response are behavioural antagonists In each case a specific type of environmental stimulus "triggers" a proprioceptive reaction in the appropriate muscles, most evident as the proprioceptive component of the grasp reflex

When the cortical lesion is extensive not only is the corresponding highly developed oriented "instinctive" response to the environmental stimulus lost, and its antagonist reaction facilitated, but a subcortical representative of the lost reaction also makes its appearance The subcortical response is a simpler reaction no longer, oriented to the source of stimulus, and it requires a more coarse stimulus Thus the grasp reflex, a subcortical response, replaces the delicately oriented "instinctive grasp response" In common with released reactions the response now requires a heavy contact stimulus, involves more muscles, and persists longer after the stimulus The corresponding proprioceptive response becomes more prominent and more persistent All further attempt to move the limb is impeded for a time after any contact with the palm of the hand In some cases not only the arm but also the leg on the same side stiffens in response to any coarse contact with the hand This is the disorder called "tonic innervation" by Wilson and Walshe (1914) Similarly, with large posterior-cortical lesions, a moving stimulus in the "hemianopic" visual field induces an eye movement which the patient cannot make voluntarily, and the deviation of eyes and head, once elicited, lasts a long time This is tonic innervation of the eyes and head

Tonic innervation of this kind is the reason for persistence of abnormal attitudes as a result of purely cortical lesions The pattern of extended fingers in an extensive parietal-lobe lesion, for example, is identical with that seen in athetosis, and it can be called "athetoid" It is not athetosis as we have defined it, for there is no essential

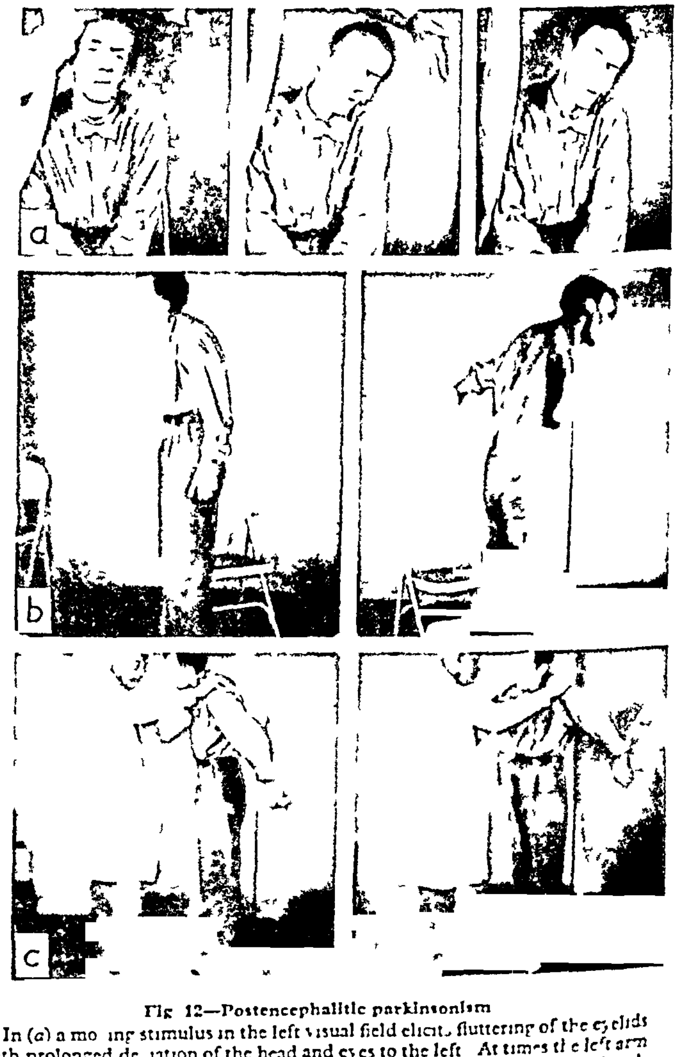

Fig 12—Postencephalitic parkinsonism

In (*a*) a moving stimulus in the left visual field elicits fluttering of the eyelids with prolonged deviation of the head and eyes to the left At times the left arm became retracted and abducted during walking (*b*) This posture appeared with passive rotation of the patient to the left (*c*) conflict, and the attitude is transitory and unidirectional (overextended in parietal lesions, overflexed in frontal lesions).

The distinguishing feature of true athetosis is that two opposing reactions to the same general type are released together. Thus, in the athetotic hand a heavy moving contact stimulus with the centre of the palm induces a coarse type of grasp reflex, and a similar contact with the dorsum of the fingers induces an extension of the fingers and wrist (Denny-Brown 1950, 1958). A heavy contact with the sole of the foot leads to a tonic foot response, and a light moving contact applied distally on the sole of the foot causes an extension of the toes with fanning. A combination of such stimuli reproduces the same alternating swings of movement in foot or hand that occur spontaneously as athetosis in the same patient. Their long persisting tonic proprioceptive after-action heightens the existing rigidity to determine the corresponding dystonic attitude. In most types of athetosis the reactions in the hand are biased in favour of avoiding, and those in the foot in favour of grasping. This pattern is that of the underlying hemiplegic dystonia. Coincident with the release of facilitated grasping and avoiding reactions, the muscles activated by these reactions are found to exhibit plastic stretch responses. The condition that has determined release of coarse contact responses has also led to over-sensitivity of the proprioceptive reactions normally triggered by contact stimulation. The conflict of stretch reactions represented by plastic rigidity parallels the antagonistic contact reactions.

In the rigidity and tremor of parkinsonism the same factors are operative, for a distally moving contact stimulus in the palm of the hand prolongs the flexion phase, and on the dorsum of the fingers it lengthens the extensor phase, of tremor. In many cases of arteriosclerotic parkinsonism without tremor a double stimulation of both dorsum and palm of the hand by a distally moving contact with the examiner's hands will induce 3–20 beats of typical parkinsonian tremor.

Patients with postencephalitic dystonic states often show the phenomenon of "oculogyric crisis." In such a patient, instructed to look forward, a coarse moving stimulus in the sensitive visual field (as in fig. 12*a*, where the upper left field is sensitive) may induce a slow tonic deviation of the eyes towards the stimulus, followed by persistent tonic innervation of gaze in that direction for a half to two minutes, associated with the fluttering tonic closure of the lids typical of spontaneous oculogyric crises. It was also noted that at times this patient walked with the left arm stiffly extended behind him, and the hand tightly clenched (fig. 12*b*). At other times the left arm was semiflexed in front of him, with parkinsonian tremor. The adequate stimulus for this abnormal extension of the arm was rotation of the head (or whole patient) to the left (but not to the right). The change in arm posture associated with passive rotation to the left is shown in fig. 12*c*. This extended retracted posture of the arm for long periods also occurs in other types of segmental dystonia affecting the arm, causing it to be strongly flexed when lying supine, and gradually overextended and retracted when the patient stands or leans forward with the face downward. The operative stimulus with long-lasting effect is labyrinthine.

Cocontraction of antagonists during attempted voluntary movement in athetosis and chorea was thought by Wilson (1925) to represent the primary disorder of motor function in these states. Our investigation indicates that each such spasm is an exaggeration and conflict of the normal reflex factors essential for all movement. If it is agreed that projected tactile and visual grasping and avoiding reactions are an essential substrate for all projected movements of the upper limb, and as such are the basis of learned purposive movements of the hand in the infant, this special difficulty with "willed" or "voluntary" movement disappears.

Some further understanding of the fundamental physiological factors that are in conflict is to be gained from animal experiments.

Lesions of the Basal Ganglia in the Monkey

It is possible to produce bilateral electrolytic lesions up to 3 mm. in diameter in the caudate nucleus, putamen, or globus pallidus of the monkey without any obvious effect on behaviour. We have ourselves in Boston confirmed in this way the observations of Ranson and Berry (1941), Kennard and Fulton (1942), and Laursen (1955). In this respect the observation of Carpenter et al. (1950) regarding the necessity for destruction of at least 20% of the volume of the subthalamic nucleus to produce symptoms evidently holds for these other structures.

Caudate Nucleus

Bilateral destruction of the caudate nucleus in the monkey produced by suction through a small incision in the prefrontal region just rostral to area 8 resulted in a remarkable change in behaviour. From the first recovery from anæsthesia the animal showed restless pacing movement up and down the back wall of the cage, facing the wall, whenever the examiner entered the room. Within a few hours this behaviour alternated with a few steps to the left side of the front of the cage to look out, then to the back wall, then again to the front of the cage, and so forth six or eight times, and then there was renewed pacing up and down facing the back wall. This type of restlessness continued day by day. On the third postoperative day it was observed that if the examiner put a hand or other object on or near the door the animal turned immediately and jumped at the object, and then jumped back to the back of the cage and continued pacing as before. In the following twelve weeks the pacing to the door gradually became transformed into a circling of the cage, always pausing momentarily at the same place near the door, sometimes pausing once to face the back wall but often only pausing to look at the wall. If the monkey was excited the full automatisms were repeated in the form they first appeared. Except for these abnormal movements there was no change in reflexes, though it was difficult to obtain instinctive grasping or avoiding responses in the mouth, hands, or feet.

Hyperactivity following destruction of the caudate nucleus has been viewed (Mettler 1942) as equivalent to that which follows bilateral frontal ablation. There is, however, an important distinction. In earlier work we found that hyperactivity after frontal-lobe ablation was determined by compulsive touching. The animal with hyperactivity after bilateral caudate lesions was entirely different. It too conducted a compulsive behavioural prominence, but this was related entirely to the presence of others—usually the observer and, to a less degree, a strange monkey. It had no tactile compulsions, but instead it showed a number of visual compulsions, of which visual challenge, visual avoiding, and compulsive visual investigation were the most obvious. It follows that the caudate nucleus must normally be concerned in the integrative balance of responses to environmental contact stimuli with those of visual content.

Putamen

Richter and Klüver (19[illegible]) report an observation for [illegible] hours of a monkey in which necrosis in the caudate nucleus and putamen of both sides had occurred after a lengthy convulsive state. The animal presented a "thalamic" posture when lying on its side, with flexion of the uppermost limbs and extension of the undermost, and both upper extremities and digits were strongly flexed in other positions Neck reflexes were present

It is most difficult to place large lesions limited to the putamen In our experiments in Boston we have succeeded in placing electrolytic lesions 4 mm in diameter bilaterally in the rostral putamen, together with 2 mm lesions in the middle of the putamen, in 2 monkeys The animals thereafter always stood in a stiff attitude, but when examined in a chair they showed only a soft yielding rigidity in all limbs, without consistent abnormality of posture When suspended in space by grasping the body all the limbs stiffened, the upper in flexion and the lower in extension In walking the feet were frequently misplaced The tactile placing reaction, by which the blindfolded animal reaches out to explore a contact with hand, foot, or lip, was performed very poorly Visual placing was well performed in all limbs The grasp reflex was very intense in both hands, but instinctive oriented grasping was absent There was a marked avoiding response in both feet Hopping and optokinetic responses were brisk, and labyrinthine postures were very active when the animal was suspended We conclude, therefore, that the body of the putamen is concerned in contactual reactions, and that when these are impaired more general labyrinthine and body-contact reactions are released

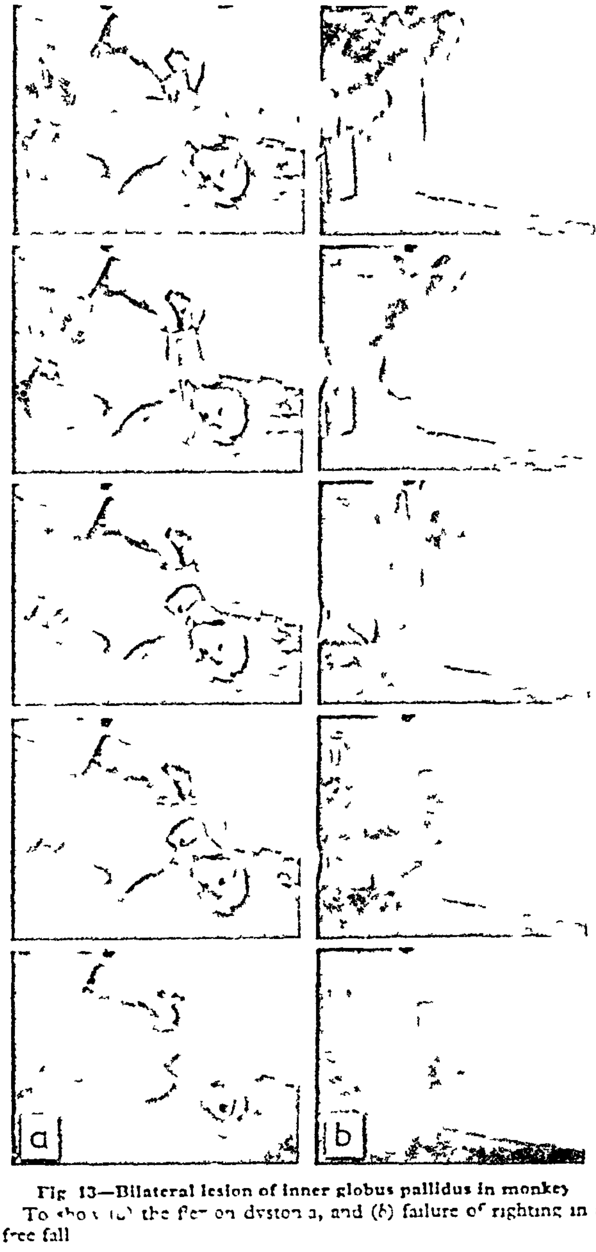

Fig 13—Bilateral lesion of inner globus pallidus in monkey

To show (a) the flexion dystonia, and (b) failure of righting in a free fall

Globus Pallidus

Electrolytic lesions of the globus pallidus, successfully placed so as to destroy most of the efferent pathway, had a most remarkable result in 3 of our monkeys Immediately after recovery from anæsthesia 2 monkeys were unable to stand, and they lay in a posture of general flexion The hands and feet were quite useless for the first three to five days, being held with elbows, knees, and wrists flexed, ankles dorsiflexed, and the fingers and toes flexed The mouth was tightly shut, and the jaws were clenched Any attempt to extend the limbs while the animal was lying encountered a resistance that caused the limb to fly back to the original posture when released (fig 13*a*) There was failure of effective righting except for an intensification of flexion of all limbs when the body lay in contact with a surface When raised in air the monkey extended the fingers and toes a little, with a series of myoclonic jerks in the flexors of the upper limbs and extensors of the neck Any contact with the lips caused the mouth and jaw to be closed tightly Food introduced into the mouth by tube was swallowed, but the face was expressionless, and the eyes, though open, appeared to fix on the examiner only with difficulty The resemblance of this posture to that observed in cases of carbon-monoxide poisoning is remarkable

During survival periods of seventeen and twenty-one days the animals learned to walk It was then apparent, that though gait was relatively normal in rhythm, the feet were often turned over and poorly placed, and the limbs were overflexed There was complete absence of both visual and tactile placing, and of tactile grasping and avoiding in both hands and both feet The hands were not used to bring food to the mouth There remained a failure of normal sequence of righting reflexes from the reclining posture After the first week the animal learned to right itself by a convulsive jerk, and then it stood in a stiff attitude, from which it fell easily If dropped in air upside down, it failed to right itself during the fall (fig 13*b*) When the monkey met an obstacle, particularly when walking into a corner, the head would be lowered and the neck flexed until the top of the head rested on the floor The animal would remain in this peculiar attitude for as long as five minutes This was traced to weakness of body-righting reflex, acting on the head

The lesions were incomplete, having destroyed about half of the inner globus pallidus, part of the related frontopontine tract, and all the ansa lenticularis and lenticular fasciculus In other animals it was found that, if any of the efferent pathway escaped destruction, the effect was very slight

The peculiar behaviour and postures of an animal with an inner globus-pallidus lesion was in this way traced to loss of all placing reactions, labyrinthine righting reactions, and optic righting reactions, in association with a very intense tonic body-contact response, leading to flexion of limbs and of both hands when the body made broad contact with a surface Another animal with lesions that on one side damaged the outer globus pallidus, and on the other severed the outer ansa lenticularis, presented a hemiplegic dystonia when lying, with extension of all limbs when suspended in air (fig 14) Placing and grasping were absent Labyrinthine reactions were overactive, and it could right itself slowly when falling blindfolded in space This indicates that the bundles of nerve-fibres entering the globus pallidus from the thalamus must serve the labyrinthine righting-reflex function that was absent in the first animals

After making these observations we found that Richter (1945) had reported the production of symmetrical necrosis of the globus pallidus in monkeys by exposure to carbon-disulphide gas His monkeys presented many of the postures described above, with marked intention tremor in addition There was plastic rigidity of the limbs Tonic neck reflexes could not be obtained, and the animal was unable to eat The necrosis of the globus pallidus was extensive In 2 of 5 animals the substantia nigra was cavitated, but this did not alter the syndrome Milder changes were found in the subthalamic and dentate nuclei, and in one animal in the hypothalamus Our own short of the external elastic membrane The raw edge of the cut was grasped with a pair of forceps, and the intima, together with most of the media, was easily peeled off from the adventitia

The circle of Willis offers special difficulties the brain arteries are even smaller and have a thinner wall than the coronary arteries It is not essential to remove the adventitia, which is very thin, and appears on histochemical examination to contain no lipids The arteries were rinsed in a physiological salt solution to clean them from adherent blood and clots, held tenaciously in the narrow lumen The arteries were transparent in the isotonic salt solution, and the degree of atherosclerosis could therefore easily be defined and recorded (fig 3 of W H O 1958)

The aortas in the previous investigation were divided into four groups according to the degree of atherosclerosis

Stage 0 no atherosclerotic lesions discernible at a magnification of ×10

Stage I fatty streaks and/or spots present

Stage II fibrous plaques and/or atheromas present

Stage III lesions as above, with additional complications—e g, ulceration, necrosis, hæmorrhage, thrombosis

The coronary and brain arteries were divided into two groups O/I (undiseased or hardly diseased) and II/III (severely diseased), corresponding to combinations of the stages as defined for aorta Since the analysis of variance of the percentage composition of aortic lipids and of the fatty-acid percentage of the aortic cholesterol esters and glycerides showed a high level of significance only for the differences between the stages 0 and I on the one hand, and the stages II and III on the other (Bottcher et al 1960), a comparison of the groups O/I and II/III should reveal most of the important trends in the course of the disease

TABLE I—COMPOSITION OF LIPIDS FROM CORONARY-ARTERY PREPARATIONS AT DIFFERENT STAGES OF ATHEROSCLEROSIS

—	Stage of disease	
	O/I	II/III
Number of samples	10	14
Average age (years)	20	47
Average weight of lipids analysed (mg) per sample	30	63
Lipids as percentage of dry tissue (mean)	20 6	22 3
Mean percentage composition of lipids		
Phospholipids	28 4	32 1
Free fatty acids	6 7	4 9
Free cholesterol	6 1	11 9
Cholesterol esters	8 8	24 6
Triglycerides	49 7	26 6
Percentage phosphorus in phospholipid fraction (mean)	1 62	2 06

No material was used from persons who had been suffering from diseases known to be associated with gross disturbances of lipid metabolism An exception was made for a circle of Willis from a diabetic patient, which was the only severely diseased circle we have met with In the specimens we have examined, the brain arteries were not affected to the same extent as were the aorta and coronary arteries As table III shows, the average age of stage O/I of the circle of Willis is much higher than the corresponding figure for the aorta and the coronary arteries

It was possible in only a few stage II/III cases to analyse lipids from the arteries of single individuals Most of these small arteries yielded no more than a few milligrammes of lipids, and the stage O/I "samples" referred to in tables IV to VII are actually pooled lipids from up to five coronary or brain arteries For stage II/III, two arteries usually yielded the required amount (at least 20–30 mg) of lipids The arteries were stored, until the arrival of complementary material, in the freeze-dried state under methanol-chloroform at −25°C

Methods of analysis of the lipids were as previously described (Böttcher et al 1959a, 1960) The prepared material was freeze-dried and extracted with methanol/chloroform (1/2), and the extract purified over a column of powdered cellulose The lipids were divided into phospholipids, free fatty acids, cholesterol esters, and glycerides plus free sterols The fatty-acid mixtures obtained from the four fractions were methylated and their compositions determined by gas/liquid chromatography over polar (maleic acid/adipic acid/ethylene glycol polyester) and non-polar (Apiezon L) stationary phases

TABLE II—COMPOSITION OF LIPIDS FROM BRAIN-ARTERY (CIRCLE OF WILLIS) PREPARATIONS AT DIFFERENT STAGES OF ATHEROSCLEROSIS

—	Stage of disease	
	O/I	II/III
Number of samples	8	9
Average age (years)	48	63
Average weight of lipids analysed (mg) per sample	21	52
Lipids as percentage of dry tissue (mean)	16 1	20 0
Mean percentage composition of lipids		
Phospholipids	58 2	37 5
Free fatty acids	5 7	4 1
Free cholesterol	9 3	14 7
Cholesterol esters	7 5	28 1
Triglycerides	20 0	16 0
Percentage phosphorus in phospholipid fraction (mean)	2 17	2 41

Statistical evaluation of the results was not considered necessary The major differences noted were all so large compared with the range of values in each group that they were undoubtedly of significance Furthermore, most of these differences between O/I and II/III arteries are in the same sense as those observed for aortas Where this is not the case, and where the differences are comparable with the individual variation, this fact is noted in the text These latter results should be regarded as preliminary indications of trends that have to be more fully examined

Results

The Lipid Composition

The mean lipid compositions of the stages O/I and II/III of the coronary arteries are presented in table I, and of the brain arteries in table II A comparison between coronary arteries, brain arteries, and aortas is given in table III

The percentage of lipids in coronary and brain artery tissue is much higher than in the aorta, both in the undiseased and atherosclerotic stages Whereas there is a threefold increase (from 3 6% to 10 9%) from stage O/I to stage II/III in the aorta (Bottcher et al 1960)—an increase which has been noted as the most characteristic feature of aortic atherosclerosis by many earlier workers—the smaller arteries have initially about five times as much lipid as the aorta and this percentage increases by a comparatively small amount with increasing severity of the disease The final value is, however, highest in the coronary arteries and lowest in the aorta These figures show a wide variation from sample to sample, and too great reliance should not be placed on them as a basis for biochemical interpretations The *composition* of the lipids obtained is, however, much more constant within each group (O/I or II/III)

TABLE III—COMPARISON OF PERCENTAGE LIPID COMPOSITION IN DIFFERENT ARTERIES

—	Aorta		Coronary arteries		Circle of Willis	
	Stage O/I	Stage II/III	Stage O/I	Stage II/III	Stage O/I	Stage II/III
Average age (years)	18	57	20	47	48	68
Phospholipids	58 0	33 5	28 4	32 1	58 2	37 5
Free fatty acids	8 0	2 0	6 7	4 9	5 7	4 1
Free cholesterol	10 1	19 4	6 1	11 9	9 3	14 7
Cholesterol esters	8 8	36 1	8 8	24 6	7 5	28 1
Triglycerides	15 0	10 6	49 7	26 6	20 0	16 0
Percentage of phosphorus in phospholipids	2 67	2 74	1 62	2 06	2 17	2 41

A striking characteristic of the lipids from the coronary arteries is the high percentage of triglycerides, which predominate over all other lipid fractions—even over sterol esters in stage II/III, in spite of the higher percentage of the latter in the more severely diseased arteries The percentages of phospholipids and of free fatty acids are not significantly different at the two stages

In the circle of Willis, the lipid composition and the changes of lipid composition show the same patterns as in the aorta, except that the fall in the percentage of free fatty acids is less marked These results are in good agreement with those of Buck et al (1954), who found that when the lipid contents are expressed as weight percentages of the cerebral artery tissue, the only differences which correlate with the disease are those in free cholesterol, cholesterol esters, and the percentage of total cholesterol which is esterified

TABLE IV—CHOLESTEROL ESTERS OF DIFFERENT ARTERIES CHANGES IN MEAN PERCENTAGES OF INDIVIDUAL ACIDS AND COMBINATIONS OF ACIDS WITH ATHEROSCLEROSIS

—	Aorta		Coronary arteries		Circle of Willis	
	Stage O/I	Stage II/III	Stage O/I	Stage II/III	Stage O/I	Stage II/III
Number of samples	12	11	3	5	3	5
Myristic (14 0)	1 8	1 3	3 6	2 0	3 0	1 5
Palmitic (16 0)	18 8	13 5	18 6	15 3	19 5	14 0
Palmitoleic (16 1)	7 1	5 4	11 0	6 6	11 9	8 0
Stearic (18 0)	4 7	1 8	5 5	2 3	4 9	3 0
Oleic (18 1)	31 0	29 3	27 5	29 7	24 1	36 4
Linoleic (18 2)	27 3	36 5	18 2	33 6	19 1	25 5
Eicosatrienoic (20 3)	1 9	2 6	0 9	1 5	1 0	1 9
Arachidonic (20 4)	2 4	4 9	2 3	2 5	1 8	3 0
Saturated	27 1	17 9	33 1	22 2	34 4	20 5
Monounsaturated	39 8	35 8	43 8	38 5	40 7	47 1
Polyunsaturated	33 1	46 3	23 1	39 3	24 9	32 4

The changes in the percentages of the lipid fractions with increasing atherosclerosis therefore show the same trends in all three types of artery (except that the phospholipid percentage does not fall in the coronary arteries)

In order to facilitate comparison of results with those of other authors, the mean percentage of phosphorus in the phospholipid fraction has been added to tables I, II, and III Most authors base their phospholipid percentage on an estimated phosphorus content, multiplied by a factor (25 or 26) which is based on a supposed average phosphorus content of 4% in the phospholipids Our phospholipids are determined gravimetrically and the phosphorus content is always much lower than 4% It is our belief that phospholipids of low phosphorus content (lipopeptides) form an essential part of the mixture and should not be neglected For comparison of cholesterol/phospholipid ratios, &c , allowance can be made for this difference in method by means of the percentages quoted

TABLE V—GLYCERIDES OF DIFFERENT ARTERIES CHANGES IN MEAN PERCENTAGES OF INDIVIDUAL ACIDS AND COMBINATIONS OF ACIDS WITH ATHEROSCLEROSIS

—	Aorta		Coronary arteries		Circle of Willis	
	Stage O I	Stage II III	Stage O I	Stage II III	Stage O I	Stage II III
Number of samples	12	11	3	4	4	5
Myristic (14 0)	3 6	3 1	3 4	2 9	4 2	2 8
Palmitic (16 0)	25 4	22 3	21 2	23 3	27 2	21 8
Palmitoleic (16 1)	5 4	5 7	6 8	6 7	7 0	6 5
Stearic (18 0)	11 4	7 3	6 0	5 3	10 3	7 2
Oleic (18 1)	33 2	37 8	46 5	41 8	27 0	33 8
Linoleic (18 2)	10 1	11 7	7 8	10 1	8 4	11 2
Eicosatrienoic (20 3)	0 7	1 1	0 3	0 5	0 3	1 2
Arachidonic (20 4)	2 7	3 4	0 4	1 7	1 9	3 6
Saturated	43 8	35 0	34 2	34 0	48 3	35 5
Monounsaturated	41 1	45 6	56 6	50 8	38 3	43 5
Polyunsaturated	15 1	19 4	9 2	15 2	13 4	21 0

TABLE VI—FREE FATTY ACIDS OF DIFFERENT ARTERIES CHANGES IN MEAN PERCENTAGES OF INDIVIDUAL ACIDS AND COMBINATIONS OF ACIDS WITH ATHEROSCLEROSIS

—	Aorta		Coronary arteries		Circle of Willis	
	Stage O/I	Stage II/III	Stage O/I	Stage II/III	Stage O/I	Stage II III
Number of samples	12	10	3	4	3	5
Myristic (14 0)	2 4	1 8	1 3	2 3	1 9	2 0
Palmitic (16 0)	20 1	17 9	14 8	20 7	19 7	16 0
Palmitoleic (16 1)	3 4	3 9	4 5	4 4	3 5	3 9
Stearic (18 0)	17 4	15 2	12 3	13 3	13 7	11 1
Oleic (18 1)	23 0	23 2	28 4	23 6	24 1	32 3
Linoleic (18 2)	18 2	17 5	27 3	26 2	27 3	22 5
Eicosatrienoic (20 3)	0 9	1 8	0 1	0 1	0 3	0 6
Arachidonic (20 4)	6 8	10 8	0 5	0 2	0 8	2 0
Saturated	43 2	37 3	32 3	39 6	39 2	33 5
Monounsaturated	27 8	28 7	36 9	30 1	30 0	38 6
Polyunsaturated	29 0	34 0	30 8	30 3	30 8	27 9

The Fatty-acid Composition

To save space, tables showing the complete fatty-acid compositions of fatty acids from all lipid fractions are not given * The acids found were the same as those shown for aorta lipids in table II of Bottcher et al (1960)

In table IV to VII comparisons have been made between the aorta, coronary arteries, and the circle of Willis with respect to the fatty acids occurring to the extent of more than 2% of the total, and to the sums of the percentages of saturated, monounsaturated, and polyunsaturated acids from each lipid fraction It can be seen that each lipid type has its characteristic fatty-acid pattern, which is in general similar to the corresponding aortic fraction, although there are a few significant differences

TABLE VII—PHOSPHOLIPIDS OF DIFFERENT ARTERIES CHANGES IN MEAN PERCENTAGES OF INDIVIDUAL ACIDS AND COMBINATIONS OF ACIDS WITH ATHEROSCLEROSIS

—	Aorta		Coronary arteries		Circle of Willis	
	Stage O/I	Stage II/III	Stage O/I	Stage II/III	Stage O/I	Stage II III
Number of samples	9	10	3	4	4	4
Palmitic (16 0)	26 5	29 8	24 6	33 1	24 3	33 2
Palmitoleic (16 1)	1 1	1 0	2 7	1 4	1 9	1 7
Stearic (18 0)	19 3	15 0	14 4	14 8	17 6	13 5
Oleic (18 1)	13 1	9 8	20 8	12 4	15 7	12 1
Linoleic (18 2)	4 7	4 1	5 5	4 4	3 2	4 4
Eicosatrienoic (20 3)	1 9	1 8	1 7	1 4	1 6	0 8
Arachidonic (20 4)	10 0	8 4	9 4	6 6	7 3	4 4
Behenic (22 0)	2 5	4 5	1 8	2 3	2 8	3 5
Docosenoic (22 1)	1 0	1 0	0 5	3 4	1 9	1 2
Lignoceric (24 0)	3 6	6 3	1 8	3 0	7 2	7 1
Tetracosenoic (24 1)	1 4	4 0	1 2	5 2	3 5	6 0
Saturated	57 3	61 6	48 5	58 0	56 3	62 2
Monounsaturated	17 5	16 6	27 5	23 5	24 3	22 5
Polyunsaturated	25 2	21 8	24 0	18 5	19 4	15 3

The *cholesterol ester* fatty acids (C E F A) of the coronary arteries change with increasing degree of atherosclerosis in the same way as do those of aorta, but the increase of polyunsaturated fatty acids is even greater, especially the rise in linoleic acid The figures given for stage O/I are the mean of three analyses, two of them from coronary arteries with a mean age of $6^{1}/_{2}$ years, and the third with mean age $21^{1}/_{2}$ years There was a considerable difference between the C E F A of these preparations at apparently the same stage of atherosclerosis The younger arteries gave a mean percentage of 13 0 for linoleic, 17 0 for polyunsaturated acids, so it seems that there is a relationship between the composition of the CEFA and age of the subject

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* Multigraphed copies of these tables may be had from THE LANCET Office, 7, Adam Street, London, W C 2

The results shown are not in agreement with those of Lewis (1958), who found a total of 81% saturated and oleic acids in the CEFA of atheromatous coronary arteries

The rise in cholesterol-ester, linoleic, and total polyunsaturated fatty acids of the brain arteries is less than in the aorta and coronary arteries Monounsaturated acids increase owing to an increase in oleic acid, whereas in aorta and coronary arteries there is hardly any change

The changes in *glyceride* fatty acids of the circle of Willis are the same as in the aorta—a fall in saturated acids balancing a rise in polyunsaturated fatty acids The coronary arteries, on the other hand, show little change in their glyceride saturated acids, the increase in polyunsaturated acids being compensated by a small (not significant) decrease in monounsaturated acids The high content of oleic acid, both in stage 0/I and in stage II/III coronary arteries, is worthy of note The composition of glycerides from the above-mentioned older example of stage 0/I was not noticeably different from the others

The *free fatty acid* composition of coronary arteries and of the circle of Willis is slightly different from that in aortas, particular features being the higher content of linoleic acid and lower content of arachidonic acid in the smaller arteries The changes with stage of atherosclerosis are also different in the coronary arteries saturated acids (in particular palmitic acid) increase, and monounsaturated acids decrease In the circle of Willis exactly the reverse takes place This is in contrast to the changes in free fatty acids of aorta, which parallel those in the CEFA and glycerides, though at a low level of significance

In the *phospholipid* fraction the summations of the fatty acids change in the same way in all three types of artery the already high percentage of saturated fatty acids in stage 0/I increases still further with atherosclerosis, there is no change or a slight decrease of monounsaturated and a decrease in polyunsaturated acids These changes, coupled with the observed variation of individual acids, can be attributed to an increase in the sphingomyelin content of the phospholipids (Böttcher et al 1960) Sphingomyelin fatty acids are characterised by a high percentage of palmitic acid, a relatively small percentage of oleic acid, and the presence of considerable quantities of acids with more than 20 carbon atoms—mainly behenic, docosenoic, lignoceric, and tetracosenoic acids (Bottcher and van Gent, in the press) The initially low percentages of these higher acids, and high percentage of oleic acid, in coronary arteries indicate that the undiseased or hardly diseased coronary arteries possess a low content of sphingomyelins

Discussion

Lipid Composition of the Three Types of Artery

The most striking feature of the lipid compositions examined is the high triglyceride content of the coronary-artery lipids It is tempting to speculate that triglycerides may be of importance in coronary-artery metabolism and disease, especially as Schrade et al (1959) have observed a high plasma-triglyceride level in patients with a history of coronary disease

Almost all the changes in the lipid compositions show the same trend in the three types of artery with increasing atherosclerosis In this sense the present results do not change the general picture of the disease built up from studies of the aorta

Fatty-acid Compositions

The rise in the average percentage of linoleic and all polyunsaturated cholesterol esters from coronary and brain arteries is not in accordance with the hypothesis which states that the formation of atheromatous deposits is due to the deposition of relatively unsaturated cholesterol esters

Cholesterol esters could be deposited from the plasma in a non-specific way, but this seems less probable than it did in the case of the aorta (Bottcher et al 1960) since the percentage of dienoic acids does not reach the same value as that in the plasma CEFA of atherosclerotic patients (Schrade et al 1959), especially as far as the circle of Willis is concerned One may conceivably speak of a barrier—a lower permeability—to polyunsaturated cholesterol esters for the brain arteries On the other hand, the diseased circle of Willis from a diabetic patient showed a high percentage (28 4%) of linoleic acid, though this was still not as high as in stage II and III aortas Most of the indications are, therefore, that higher degrees of atherosclerosis are associated with higher percentages of cholesterol linoleate

The other correlation resembling that found in aorta is the increased sphingomyelin content of the phospholipids in the more severely affected arterial wall

Changes in the glyceride and free fatty-acid compositions are too variable to admit of interpretation at present

Summary

The analysis of lipids extracted from intima/media preparations of relatively undiseased and of atherosclerotic coronary and brain arteries (circle of Willis) is described The lipids were separated into phospholipids, free fatty acids, cholesterol esters, and glycerides plus free sterols The fatty acids obtained from these four fractions were analysed by gas chromatography

The rise in lipid content of these tissues with increasing degree of atherosclerosis is not nearly so great as in the aortas, perhaps because of the initially higher values in coronary and brain arteries

The most striking difference between the compositions of these lipids and those from aortas (Bottcher et al 1960) is the high percentage of triglycerides in the coronary-artery lipids (table III) The decrease in percentage of free fatty acids with increasing severity of the disease, noted previously for aorta lipids, is much less marked in the smaller arteries Changes in lipid composition show in general the same trends in all three arteries

In the cholesterol-ester fatty acids, an increase in the percentage of linoleic acid (and polyunsaturated acids in general) with increasing severity of atherosclerosis was observed, as in aorta lipids, although the increase is less marked in the circle of Willis

Changes in the composition of phospholipid fatty acids indicate an increasing content of sphingomyelins in the phospholipids in atherosclerosis, as in the aorta Glycerides and free fatty acids show characteristic differences from those of the corresponding fractions of aortic lipids (for example, a higher oleic-acid percentage in coronary-artery glycerides and a lower arachidonic-acid content in the free fatty acids of both smaller arteries), which may be of biochemical significance

To reveal gross trends, the aorta may often be taken as a reasonable model for studies of atherosclerosis, but entire reliance on the information yielded may obscure important differences in detail existing in the smaller

arteries—differences of which the significance has yet to be elucidated

These investigations have been made with the support of the Netherlands Organisation for the Advancement of Pure Research (Z W O) and the Netherlands Organisation for Health Research (T N O) We are indebted to the Laboratory of Pathological Anatomy at Leiden for access to the necropsy material and facilities for its dissection, and to Dr J Zeldenrust (State Laboratory for Forensic Medicine, The Hague) and Dr P M Bakker (Zuidwal Hospital, The Hague), for supplying much further material We gratefully acknowledge the skilled assistance of Mr L Barnard in the preparation of the arteries, and of Miss M Kooiman, Miss H A M ter Haar, and Mr G F G Clemens in the analytical work

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MEASUREMENT OF RESPIRATORY EFFORT AND ASSESSMENT OF A METHOD OF TREATING LOWER-RESPIRATORY-TRACT INFECTIONS IN SMALL CHILDREN

W W HOLLAND *
M B, B Sc Lond
RESEARCH FELLOW IN MEDICINE

J R T COLLEY
M B, B Sc Lond
JUNIOR RESEARCH REGISTRAR IN MEDICINE

ST THOMAS'S HOSPITAL MEDICAL SCHOOL, LONDON, S E 1

M A BARRACLOUGH
M B Lond, M R C P
LATE HOUSE-PHYSICIAN TO THE CHILDREN'S DEPARTMENT,
ST THOMAS'S HOSPITAL, LONDON, S E 1

Lower-respiratory-tract infections in children, which are a common cause of admission to hospital (e g, Holland et al 1960), comprise two main syndromes—pneumonia and bronchiolitis In bronchiolitis the respiratory airway is usually considerably obstructed, as shown by intercostal and suprasternal recession, and, at times, wheezing With the pneumonias, airway obstruction plays a less important part in the clinical picture The specific treatment of these lower-respiratory-tract infections is well described in the textbooks, but no measurements of the effects of bronchodilators have been reported This study was designed to investigate the bronchodilator effects of adrenaline in such infections

Method

Eleven children, aged 1 month to 4 years, with lower-respiratory-tract infections, were investigated

The method described by Dornhorst and Leathart (1952) for assessing the mechanical properties of lungs and air-passages was adapted for use in children Intraœsophageal pressures were recorded by means of a water-filled polyethylene tube, of about 1 mm external diameter, attached to a Hansen capacitance manometer The free end was passed through the nose into the mid-œsophageal region Trunk expansion was measured by a mercury-in-rubber strain-gauge plethysmograph, one limb of which was wrapped around the child's chest, and the other around the upper half of the abdomen

TABLE I—ŒSOPHAGEAL PRESSURES AND "EFFORT" OF CHILDREN WITH LOWER-RESPIRATORY-TRACT INFECTIONS BEFORE AND AFTER TREATMENT WITH ADRENALINE

Patient no	Age	Diagnosis	Mean intraœsophageal-pressure change (cm water)		Respiratory effort	
			Before treatment	After treatment	Before treatment	After treatment
1 (a)	5 mos	Bronchiolitis	28	15	2521	1615
(b)			16	5	1494	391
2	9 mos	Bronchiolitis	16	10	1491	1107
3	1 mo	Pneumonia	9	10	509	576
4	2 mos	Pneumonia	12	10	378	476
5	3 mos	Pneumonia	10	7	651	608
6	3 mos	Pneumonia	15	14	1716	1587
7	6 mos	Pneumonia	12	12	549	648
8	7 mos	Pneumonia	17	13	1261	848
9	2 yr	Pneumonia	22	16	1538	966
10	4 yr	Pneumonia	27	11	1121	750
11	4 yr	Pneumonia	35	23	1668	960

All measurements were made on each child within 3 hours of admission, and again on recovery Adrenaline was given by deep subcutaneous injection, 0 03 ml of 1/1000 solution per lb body-weight

The respiratory rate and intraœsophageal pressure was measured over 20-second periods of regular respiration The respiratory "effort" was calculated by multiplying the respiratory rate by the intraœsophageal-pressure swing on inspiration (McIlroy et al 1954)

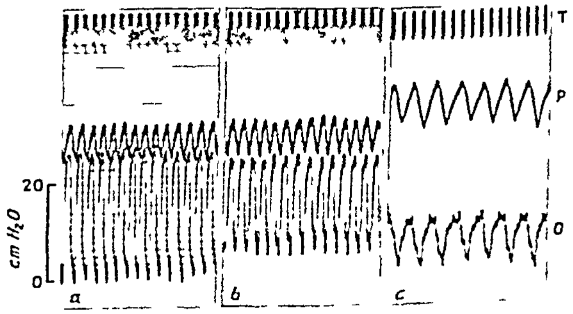
TABLE II—RELATION BETWEEN RESPONSE TO ADRENALINE, DIAGNOSIS, AND SIGNS OF RESPIRATORY-AIRWAY OBSTRUCTION

Patient no	Respiratory effort after treatment (%)	Diagnosis	Signs of respiratory airway obstruction
1 (a)	65	Bronchiolitis	Marked
1 (b)	26		
2	74		
8	67	Pneumonia	
9	63		
10	53		
11	58		
6	92		Slight
5	93		
4	126		Absent
3	113		
7	118		

Results

The results are summarised in table I In seven of the twelve tests there was considerable decrease in respiratory "effort" after adrenaline The average reduction is highly significant ($0.001 < P < 0.01$)

If these responses to adrenaline are correlated with the signs of respiratory-airway obstruction (table II), the greatest response is in the children showing the greatest degree of respiratory-airway obstruction This was also



(*a*) Before adrenaline (*b*) 5 minutes after adrenaline showing the reduction in intraœsophageal-pressure swing by about 40%, and (*c*) on recovery showing the normal pressure swing

T = time marker in seconds, P = pneumograph, O = intraœsophageal pressure

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[*] Present address Medical Research Council Statistical Research Unit, London School of H[illegible] Tropical Medicine, Keppel Street, London, W C

demonstrated by the clinical response The benefit was not limited to patients with bronchiolitis The figure shows the changes in a child with pneumonia, although, as may be seen in table I, the greatest degree of airway obstruction was in the children with bronchiolitis The improvement in condition was seen in children of all ages

Discussion

Intraœsophageal pressure is easy to measure in children, who are quite tolerant of the tube once it has been inserted In most of our cases, swings in the intraœsophageal pressure were greater than the normal (5–10 cm water) All the children were measured again on recovery, when intraœsophageal pressures had returned to normal Use of the strain gauge to record trunk expansion helped us to assess the effect of the bronchodilator substances by giving the respiratory rate and an approximate indication of tidal volume, as described by Dornhorst and Leathart (1952) We were unable to measure air flow directly as the children would not tolerate application of a mask or "box" We consider that the respiratory "effort", as expressed by the product of intraœsophageal-pressure swing and respiratory rate is a reasonable measurement of the respiratory "work", both before and after treatment

Our results show that in bronchiolitis, and in some children with pneumonia, there is an element of bronchoconstriction that can be greatly reduced by adrenaline

It is probably worth testing the effect of adrenaline in all children with pneumonia and evidence of airway obstruction

In those children in whom adrenaline was effective, it was given by injection before feeds We found that isoprenaline 1%, given via an atomiser into the oxygen tent or box for periods of 10–20 minutes in the hour, produced a response similar to adrenaline

Summary

Intraœsophageal pressures and trunk expansion were measured in eleven children with lower-respiratory-tract infections before and after injection of adrenaline The product of intraœsophageal-pressure swing and respiratory rate was taken as a measure of respiratory "effort" Those children with airway obstruction showed considerable reduction in respiratory "effort" after adrenaline

We should like to express our gratitude to the governors of St Thomas s Hospital for making a grant available from the Industrial Diseases Research Fund, to Dr J Forest Smith, Dr B D R Wilson, and Dr D G Cottom for permission to study children under their care, and to the sisters and nurses for their help in this investigation We should also like to thank Prof A C Dornhorst for much helpful advice, and Mr M Ventom for technical assistance

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> "If we have managed to rationalise the way we pay for our medical service, turning it from a jumble of sudden, catastrophic expenses and haphazard charity into a regular number of shillings per week, is it ludicrously unreasonable to think we could do the same with our legal system? And while the analogy is to hand, if a complex hospital operation can be set up when necessary in a matter of hours, is it so youthfully impetuous to suggest that legal cases ought to get to court before the passage of years and the advance of old age have wiped the witnesses' memories completely blank?"—MICHAEL FRAYN *Guardian*, Nov 3, 1960, p 9

IS RADIOLOGICAL EXAMINATION OF THE TWISTED ANKLE NECESSARY?

J S GARFIELD
M.B Cantab, M.R C P
HOUSE-SURGEON

From the Casualty Department, St Mary's Hospital, London, W 2

THIS study was undertaken to assess the value of radiology in determining the treatment of injuries of the ankle, and to define the indications for such examination 111 patients with twisting injuries of one ankle were seen by me in the casualty department of St Mary's Hospital within twenty-four hours of injury Radiographs of the ankle in the neutral position were taken in anteroposterior and lateral projections Note was taken of the following factors

1 Age, sex, and build

2 Circumstances of the injury

   a Walking injuries, which included all twisting injuries sustained while walking on level ground, without obvious cause, due to irregularities of surface, unstable high heels, or kerbs and grass verges

   b Running injuries

   c Falling down stairs or steps

3 The type of movement of the foot and ankle at the time of injury

   a A combination of inversion, plantarflexion, and medial rotation at the ankle, subtalar, and midtarsal joints was termed an *inversion injury*

   b A combination of eversion and lateral rotation was termed an *eversion injury*

4 Disability after the injury was assessed simply by whether the patient could walk.

5 Pain, tenderness, bruising, and swelling were described in terms of severity and site

6 Limitation of movement

Results

Classification

It became clear that three groups of injuries could be defined

1 *Major fractures* —Radiographs showed bony damage requiring immobilisation in plaster to prevent displacement, or bony damage with displacement requiring open or closed manipulation and immobilisation in plaster

2 *Minor fractures* —Radiographs showed injuries such as fractures of the base of the fifth metatarsal or avulsion of cortical flakes from the malleoli, talus, navicular, or cuboid The results of treating such injuries by strapping only were in no case worse than those treated by immobilisation in plaster

3 *Ligamentous injury without bony damage* —It has been said that for satisfactory diagnosis of these injuries anteroposterior radiographs must be taken with the foot held in forced inversion or eversion after injection of a local analgesic into the painful area The demonstration of tilting of the talus has been held to be an indication for immobilisation in plaster But in a busy casualty department it was impossible to take such radiographs as a routine measure Moreover, in the few cases which were so examined there was greater tilt of the talus on the healthy side than on the injured side It was decided, therefore, to dispense with such examinations, and to treat all cases in this group simply by strapping

Analysis

The next step was to determine whether a study of the clinical features as described could indicate which patients were likely to have major fractures, which were likely to have minor fractures, and which were unlikely to have bony injury In the first group radiological examination would be a necessary preliminary for treatment, in the second and third groups it would be of medicolegal interest only

Age

The patients, aged 11–60, seemed equally liable to have major fractures due to comparable types of injury

Build

The incidence of major fractures in relation to build in patients who had " stair injuries " was

Build	*No of cases*	*No of major fractures*
Fat	10	4
Normal	24	0
Thin	13	1

Circumstances of Injury

The number of major fractures associated with each type of injury was

Circumstances	*No of patients*	*No of major fractures*
Walking injuries	37	2
Running injuries	13	0
Stair injuries	47	5
Miscellaneous	14	1

Of 25 patients of normal build who sustained " walking injuries " 2 had major fractures Thus, although fat people are more liable to major fracture, such fractures cannot be excluded by consideration of build and circumstances of injury alone

The " miscellaneous " injury which resulted in a major fracture was that sustained by a skater of normal build, aged 23, the point of whose skate was firmly fixed in the ice as he fell with eversion of the foot (Fixation of the foot to the ground at the moment of injury demands radiological examination) There is no doubt that any injury more severe than a " walking " one is liable to major fracture, and, irrespective of other factors, patients in these groups should all be examined radiologically

Type of Movement Causing Injury

As all but 9 patients in this series had inversion injuries, no conclusion was reached about the relative likelihood of major fracture following inversion as opposed to eversion injury

Disability

10 patients were unable to walk after injury, only 2 of these had major fractures The other 6 patients with major fractures were able to walk Thus disability is no guide to the likelihood of major fracture

Pain

The severity of pain did not correlate with the presence of major fracture Only near the base of the fifth metatarsal did the severity and site of the pain suggest a specific minor fracture

Tenderness

Only in the absence of tenderness can it be said with certainty that a fracture is not present, in this series those patients with the most tenderness over bony parts and soft tissues had no major fracture

Tenderness over soft tissues rather than over bony points does not exclude a major fracture, and probably the absence of bony tenderness has been wrongly relied upon in the past to exclude a major fracture Only in the case of fracture of the base of the fifth metatarsal was the localisation of maximal tenderness any sure guide to the site of fracture

Bruising

The absence of bruising did not exclude a major fracture, nor was bruising more severe in those patients with major fractures

Swelling

All major fractures were associated with swelling, and it is probably safe to say that in the absence of swelling a major fracture is not present Certainly the degree of swelling is related more to the severity of soft-tissue damage than to serious bony damage, and the cases with most swelling were not those with major fractures

Limitation of Movement

In none of the patients with a major fracture did the limitation of movement differ from those with purely soft-tissue injury

Discussion and Conclusions

Having considered the individual factors in twisting injuries of the ankle, can we define a group of clinical features which will indicate that a major fracture is not present ?

Physical signs alone appear valueless, except for those patients with no swelling at all, and it is unlikely that they will reach a doctor

The least severe circumstances of injury in this series were those of the " walking " type There were 33 patients with this type of injury, in the 0–60 age-groups, of whom 2 had sustained major fractures

The first was a man of 53, of normal build, who had suffered acute inversion of the right foot while walking in the street, and who had walked to hospital where he was found to have moderate tenderness in front of the lateral malleolus, and much swelling and bruising over the lateral malleolus and dorsum Radiographs showed a horizontal fracture through the upper part of the lateral malleolus, with lateral and backward displacement of the lower fragment

The second was a man of 26, of normal build, who had had an inversion injury while walking along a station platform He had walked to hospital where he was found to have much tenderness and moderate bruising over and above the lateral malleolus, gross swelling of all aspects of the ankle, and moderate swelling over the lower third of the leg Radiographs showed a spiral fracture of the lower third of the fibula

Excluding the 2 patients with fractures of the base of the fifth metatarsal, there were therefore 31 patients, below the age of 61, who sustained " walking " injuries Analysis of the abnormal physical signs in this group shows

Bruising	*Tenderness*	*Swelling*	*No of patients*	*No of major fractures*
+	+	+	6	2
–	+	+	11	0
–	+	–	11	0
–	–	–	2	0
+	–	+	1	0

Thus only 6 patients had a combination of moderate (or severe) tenderness, swelling, and bruising, these including the 2 cases of major fracture All the other patients in this group lacked one or more of these abnormal physical signs

Therefore clinical features alone give an unequivocal guide to diagnosis in three groups of cases

The absence of any swelling is a firm indication of the absence of any significant bony or ligamentous damage whatever the circumstances of injury

Tenderness localised to the base of the fifth metatarsal is a sure indication of fracture in this site only

The absence of moderate tenderness, bruising, or swelling in a patient under 61 who injures the ankle while walking is a good indication that there is no major bony injury

In this series of 111 cases there were 41 patients in these groups I would suggest that patients in any of these three groups do not require radiological examination for the determination of treatment, such cases may well be treated by the general practitioner without reference to hospital

Summary

111 cases of injury to the ankle were studied clinically and radiologically.

It is possible clinically to define three groups in which radiological examination is unnecessary for determining treatment.

In the remaining cases clinical features give only an inaccurate guide to the nature of the injury, and in these radiological examination is necessary.

It seems that the whole question of the diagnosis of ligamentous injuries of the ankle requires re-examination.

I should like to thank Mr G. L. W. Bonney for much help and advice in the preparation of this paper.

VOLUME REGULATION AND RENAL FUNCTION IN ANALBUMINÆMIA

H. BENNHOLD
M.D.
PROFESSOR OF MEDICINE IN THE UNIVERSITY OF TÜBINGEN AND DIRECTOR OF THE MEDICAL CLINIC

D. KLAUS
M.D.

P. G. SCHEURLEN
M.D.

MEDIZINISCHE UNIVERSITÄTS-KLINIK UND POLIKLINIK, TÜBINGEN

DURING the past few years, we have had under observation a brother and sister who, because of a recessive gene, have a complete lack of serum-albumin (Bennhold et al. 1954, Bennhold 1956, Bennhold et al. 1958, Bennhold and Kallee 1959). These two cases of analbuminæmia show no disturbance of water and electrolyte balance, and are clinically healthy, though the plasma osmotic pressure is reduced from the normal of 25–30 mm. Hg to 10–14 mm. Hg.

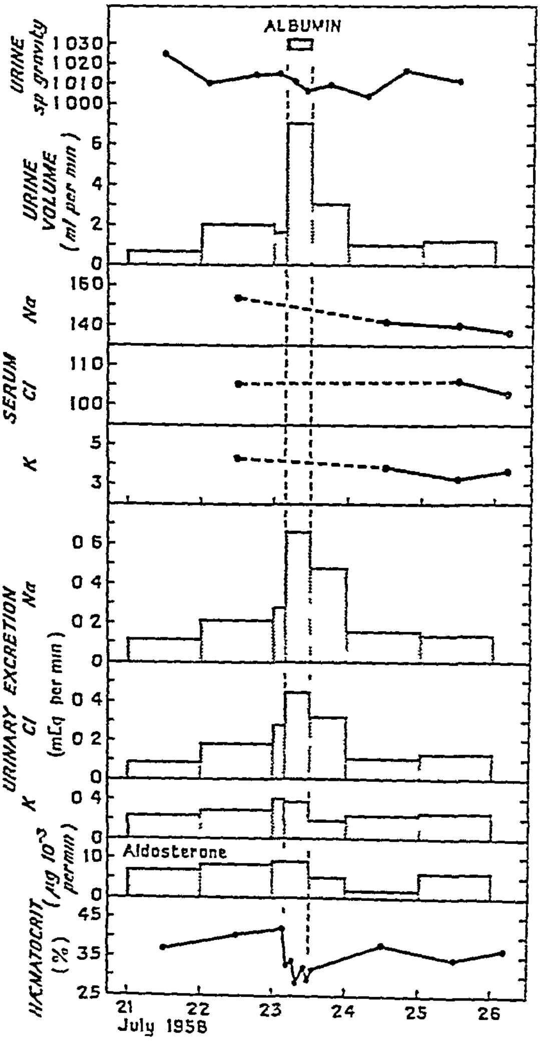
Our examinations showed that this low osmotic pressure is compensated by a marked drop in the capillary hydrostatic pressure, so that capillary tests showed some noteworthy findings. The hydrostatic pressure in the glomerular capillaries is lowered, with the result that glomerular filtration is at the lower limit of normal (see table). Normal glomerular filtration is maintained, because the renal blood-flow is already reduced in the preglomerular vessels, as shown by the reduction in renal plasma-flow. 2 days after the infusion of 150 g. of human albumin in 3000 ml. isotonic glucose-saline solution, the plasma osmotic pressure rose to an average of 20 mm. Hg, at the same time the renal blood-flow increased. Since the cardiac minute-volume, measured by the method of Broemser and Ranke, showed no change at that time (3600–3200 ml.), it may be assumed that the adaptation of the renal blood-flow to the lowered osmotic pressure is mainly brought about by vasoconstriction of the afferent arterioles.

RENAL HÆMODYNAMICS, AND WATER AND ELECTROLYTE EXCRETION IN ANALBUMINÆMIA. TESTS UNDER CLEARANCE-CONDITIONS, 1 DAY BEFORE AND 2 DAYS AFTER INFUSION OF 150 G. HUMAN ALBUMIN CORRECTED TO 1·73 SQ. M. BODY-SURFACE

—	Day 1	Day 2	Δ (%)
Urinary concentration (mEq per litre)			
Sodium	152·5	152·0	
Chloride	124·1	132·1	
Potassium	13·0	13·9	
Urinary output (μEq per minute)			
Sodium	722·0	466·0	
Chloride	589·0	404·0	
Potassium	61·8	42·5	
Urinary clearance (ml. per minute)			
Sodium	4·58	3·09	−32·5
Chloride	4·94	3·58	−27·5
Potassium	13·75	12·30	−10·5
Water	4·74	3·05	−35·6
Extraction fraction (%)			
Sodium	4·89	4·01	−18·1
Chloride	5·26	4·64	−11·6
Potassium	14·7	16·0	− 8·9
Tubular reabsorption			
Sodium	95·1	96·0	− 0·8
Chloride	94·3	95·7	− 1·5
Potassium	84·8	83·6	− 0·9
Water	95·1	96·3	− 1·1
Inulin clearance (ml. per minute)	93·7	77·1	−17·7
p-amino-hippuric-acid clearance (ml. per minute)	243·0	334·0	−37·1
Filtration fraction (%)	35·6	23·2	−40·0
Serum-albumin (g. per 100 ml.)	0·03	2·34	

Δ% = difference, expressed as a percentage, between values on day 2 and day 1.

Balance studies were made on two occasions, a year apart. During each study, an intravenous infusion of 150 g. of human albumin in 3000 ml. of isotonic glucose-saline solution was given over a period of 8–9 hours. These studies showed that in analbuminæmia the isotonic expansion of the extracellular space is balanced by a rapid diuresis (see figure). In a healthy person given isotonic or hypertonic albumin solution only a water diuresis results (Strauss et al. 1951, Smith 1957), but in the analbuminæmic patient there is an additional Na⁻ and Cl⁻-diuresis, so that the water and sodium chloride given is excreted within 24 hours. In analbuminæmia,



Urine-volume, electrolytes in serum and urine, aldosterone-elimination and hæmatocrit values before, during, and after albumin infusion on July 23 (150 g. human albumin in 3000 ml. isotonic saline glucose solution, given from 12 noon to 8.15 p.m.)

aldosterone excretion is normal, it decreases after the albumin infusion There is a definite time-lag, however, between maximum sodium diuresis and a fall in aldosterone excretion (see figure) Clearance studies showed that during the albumin-lack the tubular reabsorption of extracellular electrolyte and of water is diminished In analbuminæmia, therefore, even small quantities of isotonic saline (200–300 ml) cause a considerable sodium-chloride diuresis To achieve equally high excretion fractions in a normal person, saline infusions either 8–10 times greater in volume or 3 times more concentrated would be needed (Strauss et al 1951, Smith 1957, Ladd 1951a, 1951b)

The lowering of the capillary hydrostatic pressure and the rapid sodium-chloride diuresis resulting from small volume changes explains why, as is described in detail elsewhere (Scheurlen and Klaus 1960), in analbuminæmia, no disturbance of the water and electrolyte balance takes place, in spite of the very low osmotic pressure

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COLD INJURY AMONG CHILDREN SEVERELY ILL IN THE TROPICS

D C MORLEY
M A , M D Cantab , D C H
ASSOCIATE LECTURER IN PÆDIATRICS, UNIVERSITY COLLEGE, IBADAN
From the Wesley Guild Hospital, Ilesha, Nigeria

COLD injury in small infants, as described by Mann (1955), Mann and Elliott (1957), and Bower et al (1960), is now well recognised by doctors looking after small children in temperate climates Nassau (1948) also showed that cold injury can arise in subtropical areas, such as Palestine In the Wesley Guild Hospital, kwashiorkor accounts for a sixth of all the children admitted A fairly common syndrome in such children is a slow pulse-rate and more than the usual lethargy This had been noted for more than a year before it was discovered to be sometimes associated with a subnormal temperature In this paper I shall describe the condition of low temperature, or cold injury, in older children

The Study

During July–September, 1958, I took the temperature of all children who felt cold, using a low-reading clinical thermometer Any child found to have a temperature below 95 F (35 C) was considered to have cold injury During the three months 18 such children were seen among the 315 admitted to the children's ward, in addition 1 child was seen in a village hut Table I gives some details of these children

All these children felt cold to the hand, but they could be distinguished from children with peripheral circulatory failure because the axilla also felt cold

The most unusual feature of this series is the number of older children that it includes The following case-histories are examples of subnormal temperatures in such older children

TABLE I—SUBNORMAL TEMPERATURES IN 19 NIGERIAN CHILDREN (JULY–SEPTEMBER, 1958)

Diagnosis and no of cases	Ages of children	Lowest recorded rectal temperature (F)	Outcome—Living or dead
Kwashiorkor (8)	8 yr , 7 yr 6 yr , 3 yr , 2³/₄ yr 2 yr , 1 yr , 1 yr	93 4, 92 0, 93 1, 91 4 92 6 91 6 94 8 91 1 *(33 3–35 8 C)*	5 living 3 dead
Acute diarrhœa (5)	2 yr , 1¹/₂ yr , 1 mo , 1 mo , 1 mo	94 2, 93 8, 91 2, 94 6, 93 2 *(34–34 8 C)*	1 living 4 dead
Acute osteomyelitis (2)	3 mo , 11 days	93 6, 93 1 *(34 1–34 2 C)*	1 living 1 dead
Sickle - cell anæmia (1)	7 yr	91 4 *(33 C)*	1 living
Other conditions (3)	35 days, 17 days, 11 days	91 6 94 8, 92 1 *(33 6–34 8 C)*	2 dead 1 living

Case 1 —A Yoruba girl of 8 years was seen in a village in which the hospital is undertaking a longitudinal study of a group of children The mother was mentally unstable, her husband had left her, and the family would not assist her The child had first been seen in 1957 with œdema, puffiness of the face, and the skin changes of kwashiorkor, her mother had been supplied with protein supplements, and the child's condition had temporarily improved The protein foods were given intermittently over the next year without much cooperation from the mother, the child's condition deteriorated, and she started to have diarrhœa towards the end of July, 1958, As she was not brought to the dispensary, I visited her house in the village She was found lying semi-conscious by the embers of a fire, with only one small piece of cloth over her She was taken to the dispensary where rectal temperature was found to be only 93 4°F (34 1°C), an attempt was made to warm her up but she died eight hours later

This was the only child in this group who was seen with hypothermia in her home and not in hospital, but this is not surprising as doctors in this country rarely get an opportunity of seeing children in their homes

Case 2 —A boy aged 2 years, with the typical appearance of kwashiorkor, was brought from a village 30 miles from Ilesha by his parents He had œdema, and small areas of skin changes of the " enamel paint " type 3 days after admission to hospital his temperature dropped to 94 6°F (34 8°C) He was warmed up, but his temperature was unstable for a further five days He was sufficiently improved to be discharged home after fifteen days He was seen only once as an outpatient, and at that time he was recovering well

Case 3 —A 7-year-old boy was admitted comatose and apparently moribund His parents gave a history of eight hours' coma, and they had noticed he had become cold in the night His hæmoglobin was 18% (2 7 g per 100 ml) He was given an immediate blood-transfusion, and soon recovered consciousness He was apparently well within twelve hours, and was discharged on the third day Examination of his blood had shown a high proportion of sickled cells

The main feature of interest in this group is the number of children, over a year old, with subnormal temperatures In many of these children the ability to maintain body temperature seemed to be lost for several days Their temperatures repeatedly fell unless they were well covered with blankets, and for several an electric blanket was used as a temporary external source of heat

The child in temperate climates depends for warmth on a heated house and an adequate supply of clothing

TABLE II—MONTHLY MEAN MAXIMUM AND MINIMUM TEMPERATURE (F) FOR 1958, AT OSHOGBO, 25 MILES FROM ILESHA

—	Jan	Feb	Mar	April	May	June	July	Aug	Sept	Oct	Nov	Dec
Maximum	92	94	93	89	85	86	84	82	83	85	87	90
Minimum	70	68	71	73	71	71	69	69	70	70	71	71

The children in this community live in houses where any form of heating is unusual, the temperature usually being similar to that outside (table II). The clothes worn by small children are usually cotton, although a few babies wear wool. The small child and the sick child depend on the warmth of the mother's body. Throughout the day the child is carried on her back and at night he sleeps very close to the mother, usually with the nipple in his mouth if still breast feeding. If a child is sick and the mother has a younger child on her back, she arranges for someone else to carry the baby and carries the sick child herself. Friends and relatives except her own mother are unwilling to carry a sick child. The mother appreciates the importance of warmth to a sick child and nurses in hospital may have difficulty in persuading mothers not to put small children on their backs. In many hospitals the mothers are sent away at night, but there are still a few hospitals which make it possible for the mother and child to sleep close together.

The Yoruba child or adult takes his bath regularly, and mothers usually bath their children in the morning. Water is seldom heated, and when the bath is over the mother will put the child on her back to become warm again. In hospital, too, the child may be bathed in unheated water, but the mother will not be there, or if she is she may not be allowed to place her child on her back. Really adequate bed coverings are exceptional and a poor substitute for the mother's body heat.

Table I suggests that subnormal temperature is most common in children with kwashiorkor, the acute manifestation of the protein shortage that is almost universal among the children attending hospital in this area. Lethargy is one of the most striking features of all stages of this condition and there is also much muscular wasting. The child with kwashiorkor seems to be incapable of shivering, and none of these cold children were seen to shiver. The other feature common to most of these children was prolonged diarrhœa with variable loss of fluid and electrolytes.

Discussion

The condition of subnormal temperature was commented on by Kahn (1959), who considered a temperature below 95°F to be a grave prognostic sign in children with kwashiorkor. Of 100 such cases which he described, 5 had low temperatures, and of these only 1 recovered. Kahn suggests this condition may be associated with a low serum-potassium level; such estimations were not possible in this hospital when these cases were seen.

Experiments on several species of animals (Adolph 1951) suggest that the newborn animal can survive a low temperature which would be fatal a few weeks later. In the rat the transition to the adult intolerance of hypothermia occurs at about the age of 3 weeks. The older child similarly appears less able to withstand the effects of a low body temperature.

In the cases described here it was sometimes difficult to warm the child. Hot-water bottles are not effective, and an electric blanket could apparently be dangerous because the child might be warmed too quickly and then collapse. Re-warming by close contact with the mother seems to have much to recommend it.

In the twenty months since these cases were studied an effort has been made to prevent this condition in the ward. Mothers are encouraged to keep in close contact with their sick children, and blankets are more widely used. The nurses are alive to the condition and report any child whose temperature falls below 97°F (36·1°C), low-reading clinical thermometers then being used on such children. Another 37 children have been seen with temperatures below 95°F, of whom 15 were over a year old, and of these 9 have died.

Summary

In a hospital in Nigeria 19 children were seen within three months with temperatures below 95°F. 9 of these children died. The commonest clinical diagnosis was kwashiorkor, this being found in 8 of the 19 children.

Separation from close contact with the mother is suggested as the principal reason for this condition arising in these sick children.

I wish to thank members of the children's department of King's College in the University of Durham, Newcastle upon Tyne, for their help in preparing this paper. The Nigerian Meteorological Service supplied the data on temperature at Oshogbo. This work has been assisted by the West African Council for Medical Research.

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EOSINOPHILIC PHLEGMON OF THE ALIMENTARY CANAL CAUSED BY A WORM

F. C. Kuipers
M.D. Leiden
PATHOLOGIST, MUNICIPAL HOSPITALS, ROTTERDAM

P. H. van Thiel
Ph.D. Leiden
PROFESSOR OF PARASITOLOGY, LEIDEN

W. Rodenburg
SURGEON, MUNICIPAL HOSPITAL, BERGWEG, ROTTERDAM

W. J. Wielinga
M.D. Groningen
SURGEON, MUNICIPAL HOSPITAL, COOLSINGEL, ROTTERDAM

R. Th. Roskam
DIRECTOR CHEMICAL DEPARTMENT,
STATE INSTITUTE FOR FISH INVESTIGATION, IJMUIDEN

THIRTEEN patients with a more or less localised eosinophilic phlegmon in the alimentary canal were seen in 1955–59. This lesion, which does not seem to have been described previously, appeared to be caused by a parasite identified as the larva of *Eustoma rotundatum*. Most of the patients were infected by eating slightly salted raw herring.

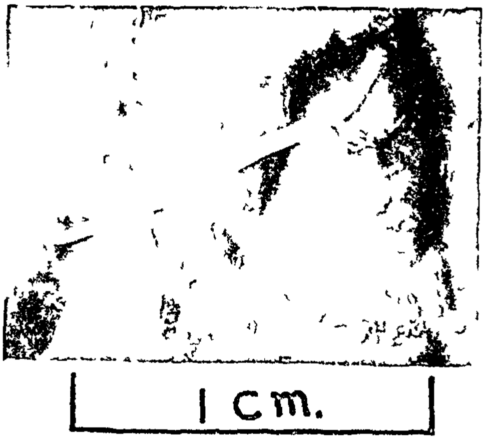
This paper describes the disease and also an investigation into the occurrence of *E. rotundatum* in North Sea herring.

Illustrative Case-report

On July 26, 1955, a man aged 51 was admitted to the surgical department of the Bergweg hospital in Rotterdam. For a few hours he had had attacks of colicky pain in the lower abdomen, rapidly increasing in severity and frequency. He had nausea, but did not vomit. There was no history of previous abdominal complaints. He had a temperature of 37·7°C (100°F), a pulse-rate of 92.

The abdomen was not distended, and moved well with respiration; there was no visible peristalsis. On coughing, pain was felt in the right lower abdomen which was also painful to percussion. Peristalsis was active. Splashing could not be elicited. No rigidity of the abdominal muscles. Tenderness of right lower abdomen. Local rebound tenderness was severe. Rectal examination was painful. The diagnosis of acute appendicitis was made—though with some reservation.

At laparotomy there was a fair amount of clear light-yellow fluid in the abdomen; the appendix was not inflamed. The distal coils of the ileum were swollen and hyperæmic. The



Ulcer of small intestine, showing larva of *Eustoma rotundatum*

serosa was covered with fibrin. About 30 cm. from the ileocolic valve there was a firm infiltration the size of a chestnut on the mesenteric border of the intestine. An ulcer crater could be felt within this area. The small intestine was not distended. The mesentery was obviously œdematous. The lymph-nodes were not enlarged.

The inflamed part of intestine was resected. The patient was given penicillin and streptomycin. The postoperative course was uncomplicated. Pathological examination of the resected specimen revealed an ulcer 1·5 cm. in diameter, out of which a worm 1·3 cm. long was protruding (see figure). The mucosa was œdematous. The serosa was also thickened and covered locally with fibrin.

Microscopically there was an eosinophilic phlegmonous enteritis with ulceration at the site of the worm. Cross-sections of the worm could be seen in the submucosa of serial sections of the specimen.

Other Patients

In twelve patients the lesion was confined to the small intestine. All were acutely ill shortly before admission, the most obvious sign being colicky abdominal pain. The previous history did not usually produce much relevant information. Only a few patients had had vague abdominal complaints beforehand.

On physical examination, apart from signs of irritation of the peritoneum, there were usually signs of an incomplete ileus of the distal small intestine.

On admission, the temperature varied between 36·2°C (97°F) and 37·8°C (100°F). Six patients had a leucocytosis, the eosinophils were counted twice, and in both cases normal figures were obtained. In eleven patients the signs were so alarming that laparotomy was carried out within a few hours after admission. Only one patient was treated conservatively for 14 days. When the symptoms did not disappear, an exploratory laparotomy was done. The inflamed intestine was resected in all twelve patients. In all the typical picture of eosinophilic phlegmon was found, and, without exception, the same parasite or—as in the case not operated upon immediately—the remnants of one were found in the centre of the lesion. A preoperative diagnosis of duodenal ulcer was made in the thirteenth case.

This patient, a man aged 43, had had gastric complaints for 6 months that did not improve with conservative therapy. The X-ray photograph supported the diagnosis of duodenal ulcer. At operation, an infiltration the size of a cherry was found 8 cm. proximal to the pylorus on the greater curvature of the stomach. The duodenum was normal. Partial gastrectomy was carried out. The lesion appeared to consist of an eosinophilic phlegmon in the centre of which remnants of the parasite were found.

The postoperative course in ten patients was completely normal. Two patients died a few days after the operation from a staphylococcal enteritis. They both received oxytetracycline in the postoperative period. In one patient a leaking of the anastomosis resulted in peritonitis on the 6th postoperative day. The patient recovered after resuturing. In three patients slight eosinophilia was established at a varying length of time after the operation. In nine patients the fæces were investigated for parasites several times, the result was negative 8 times. Ascaris eggs were found in one patient.

Ten of the surviving eleven patients were free from complaints at follow-up. 8 weeks after the first operation one patient underwent a second laparotomy for ileus caused by adhesions. No trace could be found of the original process.

Ætiology

It was not until the summer of 1958 that we were able to identify the parasite with certainty after obtaining an intact worm, by macerating a section of resected intestine for several weeks. It appeared to be a larva of one of the Heterocheilidæ. These parasites belong to the family of the Ascarides, and occur in many fresh and salt water fish and in earthworms.

A detailed history especially as regards the eating of fish was taken from the seven patients known and alive at that time. The only fish that all those interrogated had eaten was so-called "nieuwe haring" (raw herring)—sometimes as many as 20 per day. The association with the consumption of herring was still more probable when we realised that all these patients became ill between May and August. These are the months in which by far the greatest number of herrings are eaten.

After the opening of the herring season in 1959, Dr. C. F. A. Bruyning was fortunate enough to be able to obtain the parasite from a recently caught herring. It turned out to be *E. rotundatum*, one of the Heterocheilidæ (van Thiel et al. 1960). It was now practically certain that the disease was associated with herring. The occurrence of this parasite and its behaviour in fresh and salted herring was investigated by the Rijksinstituut voor Visserij-onderzoek (State Institute for Fish Investigation). It soon appeared that North Sea herring were highly infected with larvæ of *E. rotundatum* and that the degree of the infection increased with the length of the herring—i.e., with its age (see table). In freshly caught herring, the larva was found in the peritoneal cavity. When some time had elapsed before the examination, some parasites were found to have migrated into the flesh.

Before consumption, the peritoneal cavity is cleaned and its contents are removed. Only the parasites in the flesh are left behind, and it is these larvæ that are likely to be the cause of the disease in man.

The methods of preservation of herring seem to play a part. In herring that are cooked on ice without further preparation, the number of larvae that migrated from the peritoneal cavity into the flesh was much higher than in herrings salted at sea.

NUMBER OF EUSTOMA LARVÆ ISOLATED BY PEPSIN DIGESTION FROM HERRING CAUGHT IN THE NORTH SEA

Length of herring	Number of herrings investigated	Number of eustoma per 100 herrings	
		In the flesh	In the gut
20–24 cm. (small)	700	0·14	5·3
24–28 cm. (average)	207	9·6	57
29–32 cm.*	184	24	560

* Herrings of this size are hardly ever eaten raw.

directly after being caught It appears that salt has a paralysing action on the larvæ. This paralysing action is directly proportional to the salt content Nevertheless a few larvæ were found in the flesh of normally salted herring

Herrings preserved in a combination of vinegar and kitchen salt are regularly eaten in the Netherlands It appeared that the maximal survival time of eustoma larvæ in this mixture was ±25 days at 0°C The larva is almost completely resistant to gastric acid

The chance of a person consuming a larva of eustoma is 0 14% with small herrings, 9 6% with larger herrings (see table) Thus one would expect far more cases of the disease from the millions of raw herrings eaten annually than the thirteen described in this article It is unlikely that there have been any other cases of the disease in the Netherlands The pathological picture is so obvious that it would be easily recognised From the results of a questionnaire sent to the pathologists in the Netherlands in January 1959, it appeared that none of them had ever seen such a specimen before Hence the first infection with a eustoma larva is unlikely to give rise to the disease picture described It is possible that the disease only develops after a second or a third worm penetrates into the intestinal wall within a period of time suitable for sensitisation to arise The clinical and histological picture could also indicate such an allergic reaction

It is also remarkable that of the thirteen patients described eleven live in Rotterdam or its immediate vicinity Rotterdam has from early times been of the most important markets for herring, and it is common practice there to eat slightly salted herring The majority of the patients questioned ate very many raw herrings Thus they ran a greater risk of becoming sensitised

Finally it seems to us that it is not impossible that this disease is observed in other countries or islands around the North Sea Although the patients described here were almost certainly infected by raw herring, the possibility remains that the consumption of other uncooked slightly salted fish may have caused the syndrome in other cases

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Preliminary Communication

TRANSMISSION OF SERUM PROTEINS FROM FŒTUS TO MOTHER IN THE RHESUS MONKEY

INDWELLING CANNULATION OF FŒTUS WITHOUT INTERRUPTION OF PREGNANCY

IT has been shown that some serum proteins (antibodies in man[1] ^{131}I-labelled albumin and globulin in monkeys[2,3]) are transmitted from mother to fœtus in utero in primates Nothing is known about the transfer of proteins from the fœtal circulation to the mother's

We report here evidence that ^{131}I-labelled albumin and γ-globulin can be transmitted, probably selectively from fœtus to mother in the rhesus monkey, in which the placental system is closely similar to that of the human and unlike that in orders other than primates To obtain this evidence, direct access to the fœtus was necessary so that the dose of ^{131}I-labelled serum proteins could be injected into the fœtus We have found that this access can be obtained at open operation in utero and that an indwelling cannula can be left in the fœtus, without the interruption of pregnancy and with the birth of normal living babies some weeks later

METHODS

Fœtal rhesus serum (15–25 mg protein) was labelled with ^{131}I (1 0–1 5 mC) at a level of less than one iodine atom per molecule[4] Three rhesus monkeys, A B, and C, weighing 4–5 kg and estimated to be 12–16 weeks pregnant were used. Each monkey was given carrier iodide in the drinking-water one day before operation, and or an intravenous injection of sodium iodide (10 mg) They were anæsthetised with thiopentone sodium followed by nitrous oxide, trichlorethylene, and sometimes ether gallamine triethiodide was used as a muscle relaxant, and progesterone (50 mg) in oil was given intramuscularly A midline incision was made in the upper or the lower segment and the liquor amnii aspirated through the unopened membranes The fœtus was exposed and the dose was injected into a placental vein in monkey A, and into the fœtal peritoneum in monkey B great care was taken to demonstrate that no leak had occurred and that the dose had not been misplaced The uterus was then closed and the warmed liquor reinjected into the amniotic cavity

After the uterus had been opened in monkey C a cannula containing heparinised saline solution was inserted into the peritoneal cavity of the fœtus through a stab incision and anchored to the sutures closing the fœtal skin The cannula was brought out through the incision in the uterus and abdominal wall, and the sealed end anchored under the skin of the mother s flank The uterus was repaired and the liquor reinjected 6 days later the sealed end of the cannula was exposed through a small skin incision and the dose followed by heparin saline, injected into it Samples of blood and liquor were taken from each monkey 1 and 4 hours after the dose and at intervals thereafter The serum proteins were separated by electrophoresis on cellulose columns and by chromatography on D E A E cellulose as described for previous experiments[3]

RESULTS

Monkey B aborted after 24 hours, no fœtal movements were felt in monkey A after 48 hours, monkey C gave birth to a normal baby 7 weeks after operation In all three cases however, the general findings in the maternal serum and liquor amnii were similar In the maternal serum radioactivity was first found in the albumin fraction 18 hours after injection, and increased in concentration in samples taken up to 8 days after operation Radioactivity in the γ-globulin fraction isolated by electrophoresis and by chromatography appeared at 24 hours and also increased in concentration in the samples taken up to 8 days later Other serum proteins were not isolated and measured individually The general electrophoretic pattern, however, showed that little radioactivity occurred in the electrophoretic fractions between the albumin and the γ-globulin In this respect the maternal serum samples were quite different from (1) the dose material (2) serum recovered from the fœtus aborted 24 hours after the dose (monkey B), and (3) serum taken from an adult and from a month-old baby up to 8 days after being given a similar dose of ^{131}I-labelled fœtal serum

Because the dynamics of the system were so complex, no attempt was made at quantitative estimation of the percentage of the dose transferred The amounts of protein transferred, however, were small

Samples of liquor taken at successive intervals after injection contained increasing quantities of radioactive iodide (presumably from catabolism of proteins in the fœtus), but virtually no radioactivity in the proteins precipitated by trichloracetic acid.

DISCUSSION

We found previously[3] that ^{131}I-labelled albumin and γ-globulin are transferred, apparently selectively, from the mother to the fœtus in the monkey The liquor amnii did not play a significant part in this transfer The experiments described above show that both albumin and γ-globulin can return to the mother There is therefore a constant exchange of these two proteins between mother and fœtus In view of the negligible quantity of labelled serum protein going from fœtus to the liquor, it seems unlikely that this is the route of return to the mother

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[1] Brambell F W R. Biol Rev 1958 33 488
[2] Bangham D R Hobbs K R Terry, R. J Lancet 1958, ii, 351
[3] Bangham D R. J Physiol 1960 150 250
[4] McFarlane A S Nature Lond 1958 182, 53

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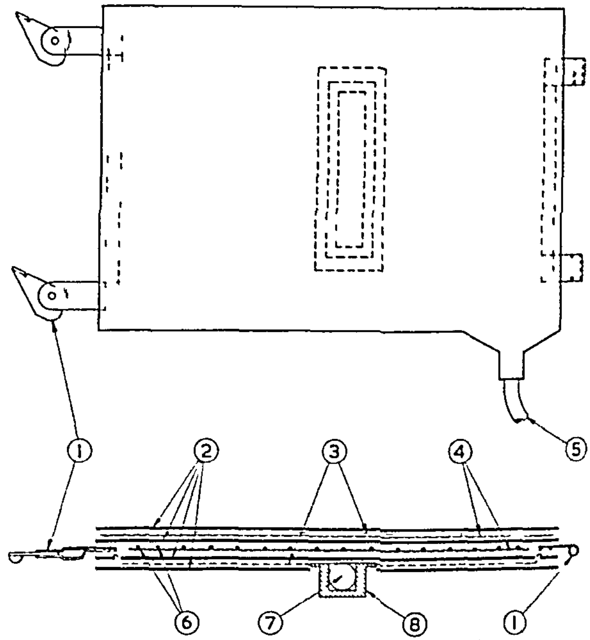

Fig 1—Plan and diagrammatic section through heater
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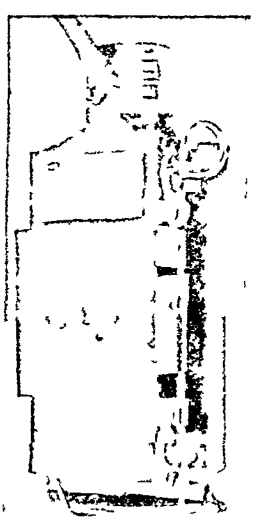

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TWO new volumes mark continuing progress towards the completion of this major urological work. Volume III, on the investigation of blood, urine, and genital secretions in genitourinary disease provides much information of fundamental importance to both clinician and pathologist In an introductory section, which will be particularly appreciated by British readers, Robinson describes the significance of abnormalities of the volume and composition of the urine, and there is a succinct account of the variations of quality of the urine in different forms of urinary disease and its relation to the symptomatology This section seems all too short and may be in places a little too dogmatic, but it is brilliantly executed and plays an essential part in conditioning the urologist to the accounts of laboratory investigations which form the rest of the volume. They are contributed by several eminent authorities in German and are detailed and comprehensive Routine methods of bacteriological and biochemical examinations are supplemented by a description of the various techniques used in hormone estimations and the concentration of antibiotics A short section is also included on the examination of the prostatic secretion and the ejaculate This accumulated information will make the volume appeal particularly to those working in laboratories attached to urological departments or clinics, and at the same time it is an essential background to the study of urinary diseases described elsewhere in the *Encyclopædia*

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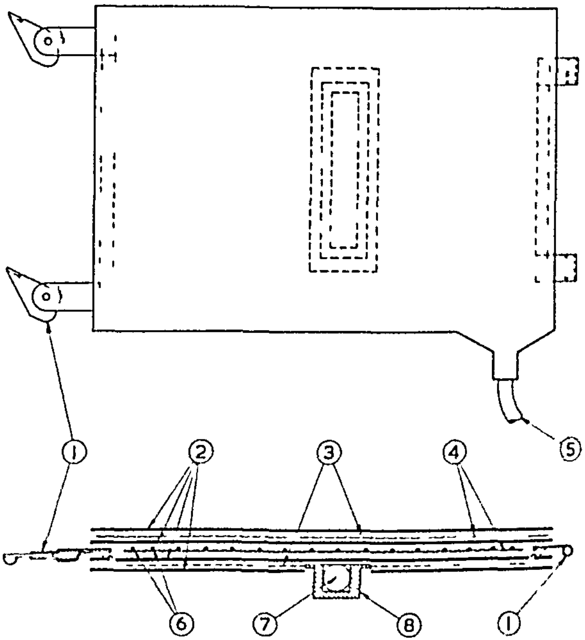

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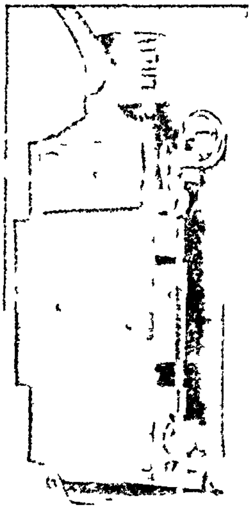

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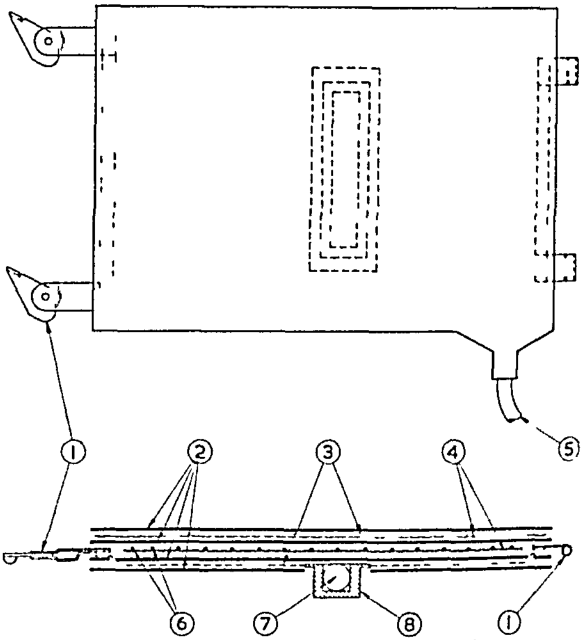

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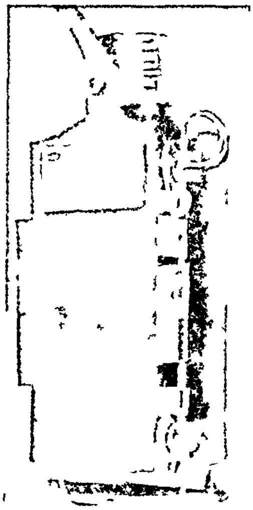

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BRITISH ORTHOPÆDIC ASSOCIATION

THE Association's annual meeting was held in Leeds and Harrogate on Oct. 27–29, under the presidency of Mr H J SEDDON

During the meeting Sir CHARLES MORRIS, vice-chancellor of the University of Leeds, described the organisation which was being set up to help the newly independent countries The Commonwealth Education Conference met in Oxford in 1959 to discuss the supply of technologists and teachers to the underdeveloped and newly independent countries It was obvious that for a long time supply would fall well short of demand, but there was great determination that something must be done and legislation (the Commonwealth Scholarship Act) had been passed to this effect 500 scholarships had been made available in this country, 250 of them to be given each year The idea was that the scholars should come here for postgraduate study after they had taken their first degree This scheme was organised by the Government but was run by the universities, which were anxious to help The newly developed countries had already had substantial sums of money to help them to develop their own universities up to the level of the first degree, and the U S.A. and Canada and other countries had been helping with this Efforts were being made to second our own university teachers to these new universities, but it was difficult to find men willing to go away, leaving families and career for three to five years Nevertheless, the scheme generally had got off to a good start

Mr SEDDON asked whether it was desirable for private arrangements along these lines to be made, such as had been made in the case of Hong Kong Sir CHARLES MORRIS replied that in such a clear-cut case the answer was Yes, and the authorities would no doubt help so long as money was available

Sir HARRY PLATT said that this was a very heartening communication But many committees were trying to carry out the same programme in these underdeveloped countries, and there seemed to be little coordination between them, each country acting independently This would lead to confusion Greater coordination would lead to economy of effort and manpower Sir CHARLES MORRIS replied that the Vice-Chancellors' Committee was in touch with similar bodies in other countries and regular meetings were held to ensure coordination.

Mr J EDELSTEIN (South Africa) said that many men came to this country from South Africa to complete their education Their own medical schools were now being formed, and the scheme mentioned was very welcome

Mr H OSMOND-CLARKE (London) asked what was the mechanism whereby a man in one of the countries could apply for a scholarship Sir CHARLES MORRIS said there was an organisation in each country for this, and he could apply to his university or the British Council There was an inter-university unit in this country to coordinate arrangements

Reviews of Books

Encyclopædia of Urology

Editors C E ALKEN, Homburg, Saar, V W DIX, London, H M WEYRAUCH, San Francisco, E WILDBOLZ, Berne Berlin Springer 1960

Vol III *Symptomatology and Examination of the Blood, Urine and Genital Secretions* Prof KARL HINSBERG, DR PHIL , direktor des Physiologischen-chemischen Institutes des Medizinischen Akademie, Düsseldorf, Prof JOSEF KIMMIG, DR MED , DR PHIL , direktor der Universitats-Hautklinik und Polyklinik, Hamburg, with JOHANNES MEYER-ROHN, DR MED , CARL SCHIRREN, DR MED , RENATE WEHRMANN, DR MED , and R H O B ROBINSON, M.D , F.R C S , St Thomas s Hospital London Pp 337 DM 118

Vol XII *Functional Disturbances* Prof ALFRED AUERBACH, University of California, San Francisco, CARL E BURKLAND, M.D , Sacramento, Prof GUSTAV-WILHELM PARADE, direktor des Städtischen Krankenhauses Neustadt a d Weinstrasse, J COSBIE ROSS, CH.M , F R.C.S , Liverpool, DONALD R SMITH, M.D , Medical School, San Francisco, WALTER W WILLIAMS, M.D , Springfield, Mass Pp 312 DM 98

TWO new volumes mark continuing progress towards the completion of this major urological work. Volume III on the investigation of blood, urine, and genital secretions in genitourinary disease provides much information of fundamental importance to both clinician and pathologist In an introductory section which will be particularly appreciated by British readers, Robinson describes the significance of abnormalities of the volume and composition of the urine, and there is a succinct account of the variations of quality of the urine in different forms of urinary disease and its relation to the symptomatology This section seems all too short and may be in places a little too dogmatic, but it is brilliantly executed and plays an essential part in conditioning the urologist to the accounts of laboratory investigations which form the rest of the volume They are contributed by several eminent authorities in German, and are detailed and comprehensive Routine methods of bacteriological and biochemical examinations are supplemented by a description of the various techniques used in hormone estimations and the concentration of antibiotics A short section is also included on the examination of the prostatic secretion and the ejaculate This accumulated information will make the volume appeal particularly to those working in laboratories attached to urological departments or clinics, and at the same time it is an essential background to the study of urinary diseases described elsewhere in the *Encyclopædia*

By contrast, volume XII is essentially clinical and deals with functional disturbances of the genitourinary apparatus The contributions of five distinguished authors include a general introduction followed by references to such varied topics as neuromuscular dysfunction and paraplegia, urogenital allergy, tetany, and male sterility With the exception of the section on tetany (in German), all are in English. There is inevitably a little overlap between the introduction and some of the later sections, but each by itself is authoritative and comprehensive Of outstanding merit is Cosbie Ross' account of neuromuscular dysfunction and paraplegia, containing a great deal of well-illustrated and practical information which those who undertake the care of patients with spinal injuries cannot afford to ignore Similarly the well-balanced account of the investigation and treatment of male sterility will be of great interest to those engaged in this rapidly expanding area of genitourinary research. Though the title of this volume may be misleading in the sense that "functional" is nowadays frequently misapplied, the contents throughout are highly practical, and make an integral and important contribution to knowledge of urogenital disease

Protein and Amino Acid Requirements in Early Life

L EMMETT HOLT, Jr, M D, department of pediatrics, New York University, PAUL GYÖRGY, M D, department of pediatrics, University of Pennsylvania, EDWARD L PRATT, M D, department of pediatrics, University of Texas, SELMA E SNYDERMAN, M D, department of pediatrics, New York University, WILLIAM M WALLACE, M D, department of pediatrics, Western Reserve University New York University Press 1960 Pp 63 $1

THIS excellent and well-documented monograph sets out clearly and concisely what is known today about protein requirements in early life Those who know the authors and their contributions to the subject will recognise the parts of the book for which they have been mainly responsible, but the integration has been admirable and the monograph reads perfectly as a whole

Beginning with the extent to which protein intake may affect the composition of the body, the authors then consider protein requirements at all ages and ways of satisfying them There is a short section on the quality of protein and the effect of heat on its nutritional value, and the latter part of the book is devoted to the requirements of aminoacids, collectively and individually The authors discuss the protein requirements, and secondarily the calorie requirements, of people living in undeveloped counties, and summarise the effects, good and bad, which may be anticipated after a large increase in the protein intake The diagrams and charts are clear and instructive All interested in infant feeding and in the wider aspects of nutrition should read this book and have it by them

Man's Posture Electromyographic Studies

J JOSEPH, M D, M R C O G, reader in anatomy, Guy's Hospital Medical School, London Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1960 Pp 88 44s

IT has been widely accepted that a man standing upright is held in that position by the "balanced tone" of the several muscles on the back and front of his legs, which, by their opposing action, fix the joints they span To those who have been taught that some "tone" is present even in muscles at rest, such sustained activity seems not unlikely and only slightly uneconomical, and the fact that no electrical evidence of its existence was forthcoming has been attributed to the difficulty of demonstrating widely separated discharges in an otherwise inert muscle mass

Dr Joseph has now shown, by the use of an extremely sensitive electromyograph, that most of the muscles in question are completely relaxed Only those of the calf, and some in the back, are contracted in the position described, which is otherwise sustained by the strength of the ligaments of the knees and hips The researches which have led to this conclusion are, in this short monograph, set out in a simple and convincing style which makes it a model for such reporting

Current Surgical Management

2nd vol *A Book of Alternative Viewpoints on Controversial Surgical Problems* Editors JOHN H MULHOLLAND, M D, New York University College of Medicine, EDWIN H ELLISON, M D, Marquette University School of Medicine, STANLEY R, FRIESEN, M D, University of Kansas Medical Centre Philadelphia and London W B Saunders 1960 Pp 348 56s

SURGICAL opinion is apt to be authoritarian, a conglomerate of tradition and top hat—thus leading to misprision But there can be no right and no wrong in a subject so full of inexactitudes, indeed, even when other things are equal, a method successful in one man's hands may prove otherwise in another's That each surgeon should develop his opinions is right, that he should advocate them is understandable, but that too often he espouses them to the exclusion of others is inexcusable In this second volume the authors pursue their civilising mission by placing side by side contrary opinions on a further selection of important controversial subjects A topical choice it is too, with repair of hiatus hernia, detection of common duct stones, treatment of breast cancer, and the significance of large-bowel polyps among the subjects discussed Many would have welcomed a discussion on the hormonal treatment of breast cancer—the pros and cons of hypophysectomy versus adrenalectomy and the place of androgens and œstrogens—but perhaps this will come in a third volume As it is, the chapter on breast cancer is confined mainly to the question of radical mastectomy, and the contributor of this chapter kills the recently agreed international method of staging almost before it has been born This seems to be the one uncivil act in a book in which 50 contributors, who know how to write, have provided much argument for the lunch table at little cost

Contributions to Obstetrics and Gynæcology

V N SHIRODKAR, M D, F R C S, F A C S, emeritus professor of obstetrics and gynæcology, Grant Medical College, Bombay Edinburgh E & S Livingstone 1960 Pp 159 37s 6d

Professor Shirodkar is best known in this country for his work on cervical incompetence The operation which bears his name is beautifully illustrated in the first chapter of this monograph, but the text is disappointingly brief Very little is said of the results, and no consideration is given to possible complications There follows a much fuller chapter on prolapse, and a number of criticisms are made of the Manchester-type operation pioneered by Donald and Fothergill Shirodkar believes that this operation is based upon an imperfect understanding of the ligamentous supports of the uterus, and he describes the modifications which he has introduced His description is supported by an excellent series of photographs and diagrams A 95% success-rate is claimed for his operation For the 5% of failures Shirodkar describes a very elaborate fascial sling operation

Further chapters are devoted to the surgery of blocked fallopian tubes and to surgical techniques for fashioning an artificial vagina The remainder of the book consists of summaries of various papers by the author There is no obvious connection between most of these items, and some are very brief

French's Index of Differential Diagnosis (8th ed Bristol John Wright 1960 Pp 1124 126s)—That this book should be approaching its fiftieth birthday (it first appeared in 1912) is sufficient tribute to the originality of its first author and to its perennial popularity and value as a work of reference It is still without a rival in its class The new edition, again ably edited by Dr A H Douthwaite, looks much like its predecessors, but the text has been widely revised and many new illustrations are included The articles, by 20 hands, maintain the expected high standard, with only very occasional lapses In the article on incontinence of fæces, for example, no mention is made of fæcal impaction, which must be far commoner than any of the causes mentioned Incontinence of urine, too, is now such a common condition in an ageing population that it might merit a main article to itself in the next edition Perhaps that will appear in time to start this unique book on its second half-century of useful life

The Diabetic ABC (12th ed London H K Lewis 1960 Pp 82 5s 6d)—In the new edition of this well-known book by Dr R D Lawrence a short section has been included on the use of the sulphonylureas, but phenformin is not mentioned It is perhaps more of a defect now than formerly that the red portions of the line ration scheme include a set proportion of protein to fat, so that it is hard to vary them independently of each other This is still possible, however, with this book if the 5-gramme ration scheme is used, although the recipes are not designed for this method In the soup recipes the amounts of the ingredients are specified without reference to the volume of soup to be prepared This book has in the past been the mainstay of countless diabetics, and with its wealth of sound practical advice it will preserve that role

Demographic Yearbook 1959 (11th ed New York U N Statistical Office Pp 719 Clothbound, 71s, paper, 57s Obtainable from H M Stationery Office, P O Box 569, London, S E 1)—The special topic covered is natality statistics from 1940 to 1958 The data show an annual population gain in the world of 48 million For the first time, an attempt has been made to differentiate the statistics according to their degree of reliability

THE LANCET

LONDON 26 NOVEMBER 1960

Criminal Justice: 1960

PUBLICATIONS on social subjects have flowed fast of late from H M Stationery Office Within a week or so we have had the reports on Children and Young Persons[1] and on Corporal Punishment,[2] and a draft Bill incorporating many of their conclusions Such legislative celerity must be almost without parallel Mr R. A. BUTLER, the Home Secretary, has left on one side the age-limits of criminal responsibility and provisions for children needing care or protection, partly because they are irrelevant to this Act and partly because he wishes public opinion to form[3] Much more contentious will be the positive decision not to reintroduce corporal punishment.

The Advisory Council on the Treatment of Offenders, a broadly based body,[4] came to a unanimous conclusion on this after initial disagreement. Their report observes that testimony was notable for its conflicting nature but pays tribute to the medical evidence, saying that " there was far greater unanimity in the views expressed to us by psychiatrists than in those expressed by members of any other profession " These views, in substance, were accepted by the Council, and some may use anti-psychiatric prejudice to attack the report. But this testimony was a small part of the Council's evidence, and we particularly welcome their extension of the Cadogan Committee's survey[5] of flogged persons (about 3000 altogether) showing that their reconviction-rate was in general slightly higher than where corporal punishment had not been given. It is good, also to be reminded that the measure favoured by most (flogging for sexual and violent crimes) would put the clock back not twelve years but a hundred and that the present demand for its return is the subject of adverse comment abroad Certainly it would have been a pity, at a time when the rate of increase of delinquency shows signs of easing, if corporal punishment had been able to claim credit for a spontaneous improvement. It is an interesting commentary on our democratic process to note from the report that the general public, the judges of the Queen's Bench Division and members of the Magistrates' Association probably favour by significant majorities some form of corporal punishment, but borstal governors and probation officers seem to hold the reverse view (of nine national daily newspapers, incidentally, only the *Express* opposes the Council's conclusions) The will of the people appears this time to have taken second place to dispassionate study of the facts

The new Criminal Justice Bill proposes, as soon as facilities permit, to exclude nearly all under-21s from prison by making greater use of borstals and detention centres, particularly of the latter (The provision in the Act of 1948 preventing a lad from going there a second time[6] is to be repeated.) This will mean a change in the character of the detention centres, which will no longer be designed to give a " short, sharp shock " to a restricted group of wayward but physically healthy youths whose disorder is not persistent or deeply ingrained In fact the intensely disciplined, spartan and energetic life of the pioneer centres has altered much over the years and in future we are going to see these centres providing confinement for the young while avoiding the contamination of hardened adult offenders When the detention-centre network is established grading of schools and classification of lads (as of prisons and prisoners) will become necessary, though the Act makes no such provision Notwithstanding magisterial enthusiasm, we have held grave doubts about the effectiveness of " traditional " detention, doubts which were not assuaged by the report of 50% reconviction among these lads within three or four years of discharge.[7] But if the new centres measure up to the best that the Prison Commission have to offer, this part of the Act will be very welcome.

Extension of compulsory aftercare to young people from those centres, and eventually to a wide range of adult prisoners, is valuable and long overdue Few physicians discharge patients after long-continued inpatient treatment without periodic follow-up and check on progress What the Act does not take account of is the troubled and inadequate state of existing facilities The organisation, and the training of suitable staff, will require a good deal of thought.

One of the more surprising proposals in the Act is that any or all of the functions of the Prison Commission may be transferred to the Secretary of State by Order in Council and that ultimately the Commission may be dissolved It is hard to foresee the implications of this, but, for a time at least, it could mean little more than business as usual behind a different shop front. The Commission, over the past few years, has taken great strides, showing courage in experimenting—or allowing others to experiment—with new ideas But for hostile public opinion and money troubles, the penal scene could, we believe, have been altered even more If closer integration with the Home Office stills this independent enterprise and makes the prison service more subservient to political fancy the move will be tragic indeed. But there is some analogy here with the

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[1] Report of the Committee on Children and Young Persons Cmnd. 1191 H.M. Stationery Office 1960 See *Lancet* Nov 5 1960 p 1015

[2] Corporal Punishment. Cmnd. 1213 H.M. Stationery Office 1960 See *Lancet* Nov 19 1960 p 1149

[3] *Hansard* Nov 17 1960 col 565

[4] The members were The Hon. Mr Justice Barry Sir Charles Cunningham Mr Paul Bennett Sir George Benson Baroness Elliot of Harwood the Bishop of Exeter Mrs [illegible] Field Mr B J Hartwell, Mr J G S Hobson The Hon. Lady Inskip Mrs V Creech Jones Mr J Lees-Jones Prof Alan Moncrieff Judge Sir Basil Nield Dr J D W Pearce Rev E. Shirvell Price Prof L. Radzinowicz Mr R. G Robinson and Colonel A. E. Young

[5] Report of the Departmental Committee on Corporal Punishment Cmd. 5684. H.M. Stationery Office 1938 p 131

[6] Criminal Justice Act 1948 section 18

[7] Report of the Commissioners of Prisons for the Year 1959 Cmnd. 1117 H.M. Stationery Office. See *Lancet* Nov 12, 1960 p 1072

Board of Control, which retired with honour on Nov 1 after a century of valuable service (including the earlier period of the Lunacy Commission) The need for day-to-day supervision of mental institutions, essential in the past century, has now gone and their management should resemble that of other hospitals within the N H S Similarly, Mr BUTLER is evidently looking ahead to a wider organisation covering Home Office responsibilities for criminal justice and the treatment of offenders[8] Integrated probation, prison, and aftercare services would certainly be welcome

While one may applaud what is in this Bill, it does not make much progress towards the ultimate goal of a penal system run effectively on factually based concepts of diagnosis and treatment The conditions for securing accurate knowledge of what prisons do to men are only slowly coming about, and experimental randomising techniques will be fought tooth and nail by the judiciary But one particularly grotesque gap in our court system could be dealt with in this Act—namely, the complete ignorance of judge or magistrate regarding the outcome for those offenders to whom they give so much thought before taking decisions which make or mar the lives before them This is like a physician giving a shot of long-acting penicillin to a man with bronchopneumonia without troubling to call again—except that the judge is much less sure that his methods work Judges, like doctors, need to learn from their errors (and from their successes) and there can be no substitute for the long-term prognostic survey KRAEPELIN founded psychiatric diagnostics in this way, and there are plenty of hints that penal diagnostics might be similarly elucidated The new aftercare provisions will help greatly in this, but we believe this Act should be amended by *a clause providing that, on expiration of any period of supervision, the original sentencing authority be furnished with a report setting out, in standardised form, the offender's subsequent career with loss of remission and why, participation in the regime, behaviour during aftercare, and so on* Addressed to the clerk of the court (who would forward it if necessary) the report would be followed by supplementary ones, should the man offend again later on This measure would not only help the courts (and their views on corporal punishment point to the need of that) but would add to the interest of an onerous task and provide a source of research material

Disorders of Movement

THE functions of the basal ganglia are still a debatable part of neurology For HUGHLINGS JACKSON the corpus striatum played an important, though somewhat ill-defined, part in the organisation of movement, the lack of definition being illustrated by the fact that he was apt to speak of the neural basis of movements as being situated " close upon " or " on the hemisphere side of " the corpus striatum KINNIER WILSON's description in 1911 of progressive lenticular degeneration brought part of the corpus striatum into a sharper focus, but also heightened the contrast between the severe and disabling symptoms in man attributed to lenticular degeneration and the physiologist's failure to produce any comparable disorder by experimental lesions in animals RAMSAY HUNT in 1917 drew attention to the association between degeneration of the globus pallidus and parkinsonism, but within a few years parkinsonism resulting from encephalitis lethargica was to be attributed to degeneration of the substantia nigra This view later received the support of no less an authority than GREENFIELD Recently evidence has accumulated that surgical lesions, either of the globus pallidus or of the optic thalamus, may benefit parkinsonism

Professor DENNY-BROWN's review (concluded in our present issue) is therefore timely, and he is perhaps unique in being able to bring to this complex problem experience in clinical neurology, neuropathology, and neurophysiology As a clinician he sees the clinical condition of a patient at any particular moment as only a phase in the course of the disorder whose pattern slowly changes through the years This leads him to recognise resemblances between disorders which, on clinicopathological grounds, have in the past been perhaps too rigidly treated as distinct, or one disorder, which at a certain phase of its evolution appears quite different from another, may at a later stage come to resemble it As a neuropathologist he seeks to correlate certain clinical pictures with such pathological features as their localisation or diffuseness, acuteness or chronicity Finally, as a neurophysiologist, he regards disorders of the basal ganglia as producing not merely isolated disturbances of posture, tonus, or movement, but as *interfering with the reactions of the organism as a whole to contact and gravity, and as disturbances of its orientation in space of a kind with which the experimental physiologist is familiar in animals* Thus, DENNY-BROWN notes the involuntary movements of Wilson's disease, whether tremulous or athetotic, giving place in time to a hemiplegic posture, a terminal dystonic state which, in his experience, is always present when bilateral rarefaction or frank cavitation of the putamen occurs In time, however, this gives place to a state of mild general flexion In Huntington's chorea, too, the earliest involuntary movements pass through an athetoid phase, which again may end in a dystonic state similar to that found in a late stage of Wilson's disease

DENNY-BROWN's study of the effects of acute lesions of the putamen and globus pallidus is of particular interest He lays emphasis on the akinetic mute state of general flexion of all limbs, with pronated wrists and extended fingers, that is characteristic of severe damage to the globus pallidus and in milder cases is associated with tremor of parkinsonian type In contrast, destruction of the putamen and caudate nucleus leads to rigid flexion of the upper limbs with extension of the lower limbs, greatly intensified by suspending the patient free of contact with body surface Taking the phenomenon of athetosis as a model, DENNY-BROWN observes that the characteristic elementary postures of athetosis are also encountered in Huntington's chorea and in dystonia musculorum deformans as well as in parkinsonism, in all of which " the essential conflict between proprioceptive inhibition and excitation is of one degree and not of kind " Hence " plastic rigidity, parkinsonian tremor, and dystonia are different aspects of a conflict of released proprioceptive reactions The conflict is resolved more slowly in plastic rigidity, more rapidly and rhythmically in tremor, and not at all in intense dystonia "

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[8] *Hansard* Nov 17 1960 col 576

But these phenomena are to be understood only by taking into account the relations between the basal ganglia and the cerebral cortex Only when the nervous system is seen as a whole, with the distance receptors conveying information of certain kinds about the environment, while the labyrinths and other proprioceptors as well as the tactile receptors are concerned with more immediate adjustments of the body in response to touch and gravity, can we appreciate the interference produced by lesions of the basal ganglia with these complex interrelations and integrations

Some Causes of Œdema

METABOLIC studies with ^{131}I-labelled albumin have greatly increased our understanding of the pathogenesis of œdema, and the recognition of massive gastrointestinal protein loss in various digestive disorders has provided clinicians with a new clue to the puzzling syndrome of "idiopathic hypoalbuminæmia "[1–5] Interest in any one mechanism may obscure the fact that usually several abnormalities underlie œdema formation, and a single case studied in great detail by GROSS et al [6] at the Peter Bent Brigham Hospital, Boston, seems particularly instructive

The patient was a 59-year-old man with a two-year history of progressive generalised œdema, without either clinical or laboratory evidence of liver, kidney, or cardiovascular disease Within a few weeks of admission—despite treatment with diet, diuretics, and digitalis—his serum-proteins fell to 2 3 and his serum-albumin to 0 8 g per 100 ml The serum was then subjected to a battery of chemical tests, including immunoelectrophoresis on starch-gel, ultracentrifugation, and assay of copper-oxidase activity, and, besides the gross deficiency in albumin, these revealed several abnormalities The iron-binding γ-globulin fraction and the serum-cæruloplasmin level were decreased, a narrow intensely staining band (with a Svedberg coefficient of 7 units) migrated with the slowest-moving γ-globulins, and a persistently raised serum-cholesterol was associated first with a rise in low-density lipoproteins and later in the disease with an increase in macroglobulins in the α_2-globulin fraction The Congo-red test and gingival biopsy for amyloidosis were negative, and there was little in the blood-smear or bone-marrow to support the diagnosis of multiple myeloma The urinary excretion-rates of 17-hydroxycorticosteroids and aldosterone were moderately raised, and turnover studies pointed to increased hydrocortisone synthesis

Though the patient had no gastrointestinal symptoms, excess fæcal nitrogen excretion (2–8 g per day) suggested the possibility of plasma-protein leakage into the gut, and, by comparing immunoelectrophoretic patterns, the Boston workers identified four serum fractions in the gastric and duodenal aspirates This finding, together with lack of sustained response to intravenous albumin and blood-transfusions, justified an exploratory laparotomy, and at operation a thickened, œdematous length of jejunum was resected (Most of the small gut was engorged, œdematous, and irritable) The resected segment was tested in vitro for capacity to transport radioactive albumin from its serosal to its mucosal surface—a possible route for plasma-protein loss in the presence of ascites Though the specimen proved its viability by actively transferring glucose against an osmotic gradient from mucosa to serosa, no reverse shift of albumin was observed Neither the operation nor a subsequent peritoneojugalar shunt brought any improvement, and the patient eventually died of pulmonary œdema and peritonitis

The turnover of ^{131}I-labelled albumin [4,7] was twice studied in the course of the illness If the daily loss in plasma-radioactivity is plotted as a percentage of the radioactivity in the tracer-dose, a curve of two components is obtained In the first three or four days plasma-radioactivity falls steeply to about 10%—a result mainly of the dilution and equilibration of the injected material in the various body-fluid compartments A longer-continued and gentler slope represents the breakdown and external loss of the radioactive albumin, and it is from this that the half-life of albumin in the plasma is calculated It has been shown, however, that even carefully labelled proteins tend to have a shorter half-life than unlabelled material [8–10] Denaturation accelerates the removal of proteins from the bloodstream, and, before the introduction of new techniques, partial denaturation was the inevitable side-effect of over-iodination, heat-treatment for sterilisation, and internal radiation damage [11,12] Nevertheless, comparison of the half-lives of identical preparations of ^{131}I-albumin in the patient and in healthy controls showed that albumin disappeared from the patient's plasma about twice as fast as from the plasma of the controls, and calculations based on this finding indicated that his fractional rate of albumin catabolism was considerably increased Such an increase does not necessarily mean that abnormally large amounts of albumin are broken down Obeying the law of first-order reactions, albumin catabolism removes a more or less fixed proportion of the total body pool each day, not a fixed number of molecules [8] and the fractional rate of turnover is therefore increased when the body pool is reduced more than the breakdown-rate (as can happen in cirrhosis or proteinuria), and, conversely, it declines when the body pool is increased disproportionately to a rise in albumin synthesis It is, of course, far from easy to measure with any accuracy the albumin pool of a patient with gross œdema,

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[1] Albright, F , Bartter, F C , Forbes, A P *Trans Ass Amer Phycns*, 1949, 62 204
[2] Schwartz M , Jarnum, S *Lancet*, 1959, i 327
[3] Young, W F , Levin, B , Fowler J F , Miles, J M *ibid* 1959, ii, 85
[4] *Lancet*, 1958, ii 1000
[5] *ibid* 1959, i, 14
[6] Gross P A M Laurence J E , Bally, P , Shipp, J C , Thorn, G W *Amer J Med* 1960, 29 386
[7] Gitlin, D , Janeway C A Farr, L E *J clin Invest* 1956, 35, 44
[8] Gitlin, D *Pediatrics*, 1957, 19, 657
[9] Bennhold, H , Kalee, E *J clin Invest* 1959, 38, 863
[10] Freeman T , Matthews, C M E , McFarlane, A S *Nature, Lond* 1959, 183, 606
[11] McFarlane, A S *Biochem J* 1956 35, 746
[12] Hayter, C J *J clin Path* 1960 13, 369

effusions, and ascites, but qualitatively if not quantitatively the estimates of GROSS et al. can be accepted. These showed that their patient catabolised only 9 g. albumin per day (the normal range is 15–25 g.), but that this figure represented 13.1% of his total body pool (normal 4–6%). The state in this case contrasts strikingly with that in congenital analbuminæmia, which Professor BENNHOLD and his colleagues discuss in their article on p. 1169.

In the absence of external loss in the urine or fæces, or from exudative skin lesions, an increased fractional rate of albumin catabolism points to excessive albumin breakdown in the tissues or to albumin exudation and breakdown in the gastrointestinal tract. Neither of these processes is easily measured. Since the stomach excretes a considerable amount of $H^{131}I$ (in place of HCl) estimations of total ^{131}I activity in the gastroduodenal juices and in the fæces are of little significance, and rapid breakdown of labelled albumin by intestinal enzymes and reabsorption of the aminoacid residues, including ^{131}I-tyrosine, interfere with the measurement of albumin-bound ^{131}I. (Labelled polyvinyl pyrrolidine, recently introduced by GORDON,[4, 13] overcomes this difficulty: it has a similar molecular weight to that of albumin but it is not hydrolysed by gastrointestinal enzymes.) Another difficulty lies in our ignorance of where albumin is normally catabolised in the body. Experimental work strongly suggests that the reticuloendothelial system plays a dominant part,[14, 15] but in the Boston case attempts to inhibit reticuloendothelial-system activity by various forms of steroid therapy[16] were ineffective.

Though a raised fractional rate of albumin catabolism alone can account for hypoalbuminæmia, other mechanisms must probably operate before œdema develops. The grossly subnormal rate of albumin synthesis (9 g. per day) in the patient investigated by GROSS et al. is the more surprising since in many hypercatabolic states the body can balance increased loss by an increase in albumin synthesis. Albumin, moreover, is synthesised entirely by the liver, and not only did liver-function tests fail to reveal signs of parenchymatous damage but postmortem examination also showed that the liver was relatively healthy. Albumin hypoanabolism, however, is occasionally the sole manifestation of liver dysfunction—another reminder that, unless interpreted with great caution, "liver-function" tests can be as meaningless as body-function tests.

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The name "anonymous mycobacteria" has been given to mycobacteria, isolated from human morbid material, which are distinct from tubercle bacilli and other accepted species. So defined, the group contains mycobacteria of undoubted pathogenicity and also casual transient intruders. Pathogenic strains cannot be identified with certainty by their properties, but a mycobacterium isolated repeatedly in the absence of any other evident cause may be regarded as a presumptive pathogen. Casual anonymous strains are rarely isolated more than once from any one patient. Classification of the anonymous mycobacteria owes most to RUNYON,[24] who has defined the following groups:

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15. Katz, J., Rosenfeld, S., Sellers, A. L. *Fed. Proc.* 1959, 18, 257.
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17. *Lancet*, Oct. 1, 1960, p. 746.
18. Veall, N., Vetter, H. Radioisotope Techniques in Clinical Research and Diagnosis. London, 1958.
19. Scow, R. O. *Endocrinology*, 1951, 49, 641.
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LEWIS et al [25] report from Florida 116 cases of pseudotuberculosis due to non-photochromogens The organism was demonstrated repeatedly by culture in all cases and by smear in 70% Symptoms were similar to those of tuberculosis and included cough, loss of weight, low fever, and, in some cases, hæmoptysis Radiological appearances were indistinguishable from those of tuberculosis, and cavitation was present in 78% Skin tests with standard P.P D and a protein preparation from a non-photochromogen culture were made in 50 cases and were compared with the results in 50 cases of tuberculosis In the great majority there was a larger reaction to the homologous antigen A disquieting feature of the study was that patients with pseudotuberculosis fared less well than those with tuberculosis The cause was no doubt the inherent resistance of non-photochromogens to most chemotherapeutic agents (photochromogens are somewhat less drug-resistant), though a fair number of strains were sensitive in vitro to viomycin, cycloserine, kanamycin, and streptovaricin Of a total of 78 patients treated medically, 15 died, 44 were considered still to have active disease on discharge from hospital (27 remaining bacteriologically positive), and only 19 appeared to have overcome their infection Resection was undertaken in 37 cases and plombage in 1 Complications of surgery were rather commoner than in tuberculosis, they included bronchopleural fistula in 3 cases and hæmorrhage in 2 In 2 cases death followed operation The disease became inactive in 30 patients

Experience in Florida, as in this country, suggests that in many cases of pseudotuberculosis resistance to mycobacterial infection has previously been lowered by other chest disease or by debilitating conditions such as alcoholism or gastric resection Occasional cases in patients on steroid therapy suggest that this, too, may predispose to the infection The incidence of anonymous mycobacteria in Florida is similar to that reported for Wales by MARKS and TROLLOPE,[26] who found these organisms in 2% of new patients yielding mycobacteria on sputum culture, but only 42% of their anonymous strains were judged to be pathogenic

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"LET me introduce you to my medical adviser", people sometimes say, and in his James Mackenzie lecture to the College of General Practitioners last Saturday Dr Lindsey Batten talked about the doctor's role as adviser to his patients The doctors of Dr Batten's vintage had on the whole a very creditable medical education, with an eye to general practice, but, even so, he said, they were not taught the art of advising or urged to look forward to it as an important part of practice

Taking examples from the various ages of man, Dr Batten spoke of questions about heritable disease and marriage as illustrating his view that the doctor's job is "to advise, not to give orders or pass judgment" In pregnancy "the personal medical adviser is at least as much needed in these days of antenatal clinics and books and pamphlets for expectant mothers as he was before they existed", for somebody must be prepared to listen, explain, and advise, even if only for "the odd person who wants to know" Infant welfare—a province hard but not impossible for the practitioner to regain—carries the same need for something more than standardised advice the young mother up against infant perversities and conflicting counsel can be greatly helped by someone with quite a small fund of apposite knowledge who is not blown about by every wind of doctrine And it is the same with toddlers, with their variations on a nursery theme

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After touching on sexual instruction—part of which can very well come from the family medical adviser—and the advantage for boys and girls to feel that they have an unshockable medical friend, Dr Batten turned to invalidism of the form of disability too often called chronic neurosis Needless "distrust of a vital organ" can easily be sown and grow, and though its uprooting may require a consultant as well as a family doctor, it is a personal task for which teams and institutions are wholly unfitted If a young man thinks his heart is at fault, the effusions, and ascites, but qualitatively if not quantitatively the estimates of GROSS et al can be accepted These showed that their patient catabolised only 9 g albumin per day (the normal range is 15–25 g), but that this figure represented 13 1% of his total body pool (normal 4–6%) The state in this case contrasts strikingly with that in congenital analbuminæmia, which Professor BENNHOLD and his colleagues discuss in their article on p 1169

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[25] Lewis A. G Lasché E. M Armstrong A. L., Dunbar, F P *Ann intern Med* 1960 53 273

[26] Marks J, Trollope, D R. *Tubercle, Lond* 1960, 41, 51

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Reasons may be plentiful, but the hard fact remains that time and again the patient returns from hospital or consulting-room with questions unanswered or unasked and dark speeches unilluminated or misapprehended Once again there is only one possible source of light—the personal medical adviser Were he to disappear "there would be no public outcry for his re-establishment and the Ministry would not notice the difference The fragmentation of medicine, the adulation of teamwork, the curious belief that uniformity is somehow identical with justice, the unquestionable fact that he is, as they say, 'uneconomic'—all these militate against him His chances seem poor and yet if he goes the sum of human unhappiness, great enough already, will be greater and the satisfaction of medical practice to the practitioner will be less"

To save him, Dr Batten said, two things are needed First we must keep his image bright before the eyes of all concerned, and secondly we must not rest until we secure for him the one indispensable requirement—time Time to listen, to think, and to talk

ADENOVIRUS VACCINATION

SOME adenoviruses (notably types 3, 4, 7, and 14) are known to cause serious epidemics of respiratory diseases, mainly among military recruits and children The early studies were carried out in America, but adenoviruses have been shown to be important in this country among R A F recruits and public-school boys[1-4] Bell et al[5] found in volunteers that protection against the disease was conferred by antibody Two groups in America, led by Huebner[6] and Hilleman,[7] who were the two discoverers of this group of viruses, have shown that a formalin-inactivated vaccine containing either one type or the three most prevalent epidemic types (3, 4, and 7) confers protection against these infections by producing a specific antibody response The vaccines were prepared from adenoviruses grown on cultures of monkey-kidney cells in a similar way to that used for poliovaccine manufacture The importance of adequately inactivating the virus was indicated by Hilleman et al,[8] who inoculated volunteers with living virus and produced respiratory symptoms with conjunctivitis

Hitchcock and her colleagues[9] have now shown that satisfactory antibody responses can be achieved with low doses of attenuated adenoviruses, probably without producing symptoms They used strains of adenovirus types 4 and 7 adapted to grow in pig-kidney cells[10] The type-4 virus had had 11 passages in pig-kidney cells and the type 7 either 7 or 17 passages 13 volunteers were given type-7 virus, and in the 4 without detectable neutralising antibodies to type 7 these developed as a result of vaccination, of these 4, 2 received only 150 T C D$_{50}$ intranasally In 3 volunteers who received 250 T C D$_{50}$ of type-4 virus no neutralising antibodies developed, but in 2 who received 2500 T C D$_{50}$ antibodies did develop Some of those who received type-7 virus also showed a rise in titre against type-3 virus if they already had some antibody to type 3

In some who received the attenuated adenovirus mild symptoms developed, several of these showed no serological evidence of adenovirus infection, and since the trials coincided with an unusually high incidence of mild coryza with slight abdominal symptoms even in control volunteers, Hitchcock et al were uncertain that the symptoms were due to the adenovirus vaccine In 6 of the 8 people with serological evidence of infection with type-7 virus, this was isolated either from throat swabs or from fæces, but the virus was not present in very large amounts, and it could be transmitted only with difficulty from man to man

This work suggests that attenuated living adenovirus vaccine may be a practicable, cheap, and easy means of conferring resistance to adenovirus infections Larger-scale trials in susceptible child or recruit populations would be necessary in order to show that the method prevents epidemic adenovirus disease If it is effective its use might be considered not only in susceptible school or recruit groups but also for infants, in the hope that a significant amount of respiratory-virus infection would be prevented Respiratory infections, not all of course due to adenovirus, account for nearly 50% of all illnesses in children under 5[11]

HYSTERIA SYMPTOM OR DISEASE?

HYSTERIA, that most venerable of psychiatric syndromes, seemed, by the classic studies of hypnosis and dissociation, to be one of the most firmly founded entities Low concordance of diagnosis between physicians, however, and the frequent discovery of other disease underlying the dissociated state has weakened the concept, and Dr Eliot Slater, in a Maudsley lecture, delivered in London on Nov 18, cast the severest doubt on hysteria as a "disease"

From the basic hypothesis that monozygotic twins offered a controlled study set up by Nature, Dr Slater had constructed a survey of hysteria 12 each of monozygotic and dizygotic twins with a diagnosis of "Hysteria, code number 311" had been collected from cases seen at the Maudsley and Belmont Hospitals Not one single twin partner of either group had received a formal diagnosis of hysteria—a concordance of 0%, which, even including a doubtful case, seemed to rule out a genetic background Widening the comparison to other neuroses and to cases treated by the general practitioner brought in several twin-pairs but did not lend support to a genetic hypothesis Study of the family history brought to light no single secondary case of hysteria among parents and siblings, and no excess of psychiatric disorder of any kind except manic-depressive illness

As to the effects of environment, affected dizygotic twins were found to be at birth significantly lighter, and in youth poorer in health, than their partners A preponderance of left-handedness and ambidexterousness in affected twins also suggested a physical basis in some cases Many other early factors—parental attitude, birth order, feeding difficulties, &c —were not significantly different between the twin partners Adult bodily health,

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[1] Tyrrell D A J, Balducci D Zuman T E *Lancet* 1956 ii 1326
[2] Kendall E J C, Riddle R W, Tuck, H A, Rodan, K S Andrews B E, McDonald J C *Brit med J* 1957, ii, 131
[3] McDonald J C Wilson J S Thorburn, W B, Holland, W W, Andrews B E *ibid* 1958 ii 721
[4] Munro Ashman D Gardner P S, Taylor C E D McDonald J C *Lancet* 1958 ii 121
[5] Bell J A Ward T G Huebner R J Rowe W P, Suskind R G, Paffenbarger R S Jr *Amer J publ Hlth* 1956 46 1130
[6] Bell J A Hantover M J, Huebner R J, Loosli C G *J Amer med Ass* 1956 161 1521
[7] Stallones R A Hilleman, M R, Gauld R L Warfield M S Anderson S A *ibid* 1957 163 9
[8] Hilleman M R Hodges R E Warfield M S Anderson S A *J clin Invest* 1957 36 1072
[9] Hitchcock G, Tyrrell D A J Bynoe M L *J Hyg, Camb* 1960 58 277
[10] Guérin L F Guérin M M *Proc Soc exp Biol N Y* 1957 96 322
[11] Miller F W J Court S D M Walton W S, Knox E G Growing Up in Newcastle upon Tyne London 1960

however, was considerably poorer in affected twins and might provide a background for hypochrondriacal preoccupations

Turning to the incidence of other disorders in this group of twins, Dr Slater noted an excess of epilepsy, schizophrenia, endogenous depression, and especially personality disorder characterised by abnormal tension and anxiety, or timidity and shyness The sexual histories of most cases were full of problems and marital maladjustment Historical search for psychogenesis was unrewarding in half, and the stresses precipitating the hysterical episodes in most others were often trivial Prognosis, over some five to seven years, was surprisingly varied, and poorer than was often thought, more than half still had symptoms It seemed that disappearance from psychiatric clinics of the young hysteric was due more to disappointment than to remission Cosseting by the marital partner was associated with a lengthy illness

Dr Slater remarked that the feature emerging most strongly from his study was heterogeneity Heredity, history, diagnosis, personality, response to treatment, and outcome varied so greatly among hysterics that he doubted the existence of the condition as an entity Just as Ganser states and anorexia nervosa were thought to occur in different conditions, so, he suggested, hysterical phenomena of a more general kind were to be regarded as symptoms that might have arisen from a variety of causes Hysteria was often diagnosed where the case was obscure or treatment failed histrionic elements, lack of genuineness, or demand for (rather than acceptance of) treatment all led to this diagnosis—one which was often made in no state of emotional detachment, and one which probably indicated that the physician had not looked deeply enough

THE CASE AGAINST TRENDELENBURG'S POSITION

THE "head-low" position described by Trendelenburg seventy years ago[1] is still widely used as an aid to pelvic surgery, but the circumstances which led to its introduction have changed, and whether there is any need for this position in modern surgical practice is debatable Abdominal relaxation was difficult to achieve in Trendelenburg's day, and only by lowering the patient's head and applying several abdominal packs could the surgeon keep the intestines out of the pelvic operating field With modern anæsthesia, including relaxants, the same operative exposure can be achieved with the patient in the horizontal position

Swain[2] believes that the Trendelenburg position accounts for many cases of postoperative shock, lobar collapse, pneumonia, and venous thrombosis Impressed by the seriousness of these complications he has stopped using the position in his theatre In 100 consecutive pelvic operations with the patients lying flat he has achieved excellent accessibility and visibility of the pelvic organs, and postoperative complications have ceased to be a problem on his unit Most anæsthetists will applaud Swain's initiative, for they have long been concerned over the related embarrassment to cardiovascular and respiratory systems, particularly in obese and hypertensive patients It remains to be seen whether Swain's suggestion finds favour with gynæcologists, most of whom have been trained to operate with the patient in the Trendelenburg position

FOOT-AND-MOUTH DISEASE

FOOT-AND-MOUTH disease, which affects pigs, sheep, and goats as well as cattle, has an incubation period of 3-5 days and is spread by droplet infection, by direct contact, or by contaminated objects Almost anything which moves or can be moved from one farm to another may spread this highly communicable virus, which multiplies very rapidly in the tongue epithelium, in blisters round the mouth, or in bulbs of infected animals' heels Outbreaks in this country arise from virus imported either from nearby endemic areas in the Low Countries or France, or by contaminated meat from South America The present outbreak began at a time when huge flocks of starlings and other migratory birds cross the North Sea to winter here, but there is no evidence that they started the trouble Workers at the Foot and Mouth Research Institute at Pirbright are convinced that the virus remains infective on the feet, feathers, and droppings of starlings for many hours, but it is, of course, virtually impossible to incriminate birds in a particular outbreak Previous epidemics here have often followed explosive outbreaks on the Continent, but this year there has been no topping-up in the neighbouring reservoirs and in any case there seems to have been only one primary focus in this country Evidence from this focus was very scanty, but it is widely believed that infected meat from South America found its way unboiled into pig swill, and from pigs other stock were infected This is the other main route of spread, and farmers, possibly with other considerations also in mind, naturally emphasise these controllable sources of infection Last week the Government met some of their requests, and from Feb 1 next year imports of pork and pig offal, which are said to be inadequately inspected at the South American ports, will be prohibited

Veterinary investigation officers of the Ministry of Agriculture have already untangled much of the revealing story of the present outbreak Infected cattle from the north of England were sent to be sold at Stowmarket and later arrived in Diss and then at Norwich market, which soon became the main centre of spread in England Scotland is often spared these outbreaks, but cattle from Newcastle, sent in error to Norwich before reaching their true destination in Aberdeen, contaminated the market pens and spread the disease widely through the North-east and as far as Glasgow and the Orkney Islands Although nothing of the sort has yet happened, conceivably the greatly increased herds of wild deer in Scotland may one day acquire the infection and become a more serious and more persistent menace than hedgehogs, the only other wild animal susceptible to the virus By the end of last week there had been outbreaks in nearly 150 farms and markets, and already this will cost £500,000 in compensation In the last major epidemic in 1951–52 there were about 600 outbreaks requiring the slaughter of 85,000 animals, and it is interesting to recall that subsequent investigations showed that half the outbreaks could be traced to a single incident near Crewe

So far this year there has been little open criticism of the policy of slaughtering all infected animals and their contacts, and farmers are to be congratulated on their attitude to this harsh but essential measure Present-day vaccines are not a reasonable alternative an effective vaccine must cope with the many antigenic types of virus—the older types O, A, and C, plus 3 South African and 1 Asian strain —and provides an immunity after vaccination which is both type-specific and comparatively shortlived Though newer vaccines are being tried in South Africa, it is from the investigations at Pirbright and elsewhere that progress is most likely to come Since Brooksby's review [1] of recent knowledge of the virus, much fundamental information has come to light, and recently Bradish et al [2] studied the antigens concerned in complement-fixation tests, which are of great importance since they provide the only qualitative procedure sufficiently sensitive for the investigation of field and experimental samples Two main components are concerned one is infectious, type-specific, and about 25 mμ wide, the other, 7–11 mμ, is non-infectious, and has only disease-group specificity Bachrach,[3] comparing complete virus with the infectious nucleic acid, has shown by the tissue-culture plaque technique that single ribo-nucleic-acid molecules rather than clumps seem to be the infectious units when tested on cultures of calf-kidney But these important investigations are cold comfort for the farmer, who is concerned with an effective vaccine or other means of dealing with the endemic pools of infection which constantly threaten to spill over into the few fortunate areas of the world where virus-free stock can be raised Meanwhile, slaughter remains the only practical policy, and the apprehensive farmer behind his antiseptic moat is as effectively isolated as the Weston neighbours of Parson Woodforde when smallpox made visitation on his parish nearly two hundred years ago

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[1] Trendelenburg F Sammlung klinischer Vortrage p 3373 Leipzig 1890

[2] Swain J *Med J Aust* 1960 ii, 536

VIRAL DISEASE OF THE CENTRAL NERVOUS SYSTEM

ASEPTIC meningitis, which would formerly have been diagnosed usually as non-paralytic poliomyelitis, is now known to be often due to organisms other than polioviruses In the first trial of killed poliovaccine [4] the vaccine proved relatively ineffective against "non-paralytic poliomyelitis" This, as Lennette et al [5] have clearly shown, was not because vaccine is ineffective against non-paralytic poliomyelitis, but because most cases of aseptic meningitis with this clinical diagnosis are not due to poliovirus Subsequent extensive studies of three viral diseases of the central nervous system—paralytic poliomyelitis, encephalitis, and aseptic meningitis—have shown that some cases of all three syndromes are not due to poliovirus Although poliovirus is a well-recognised cause of encephalitis [6] it has long been known that other viruses are more usual causes In Lennette's [5] investigation, for example, although a viral diagnosis was made in only just over 20% of the cases, of those diagnosed 15% were due to Coxsackie viruses, 12% to mumps, 7% to herpes simplex, and 5% to poliovirus In a larger study Meyer et al [7] made a specific diagnosis in 72% of cases with a diagnosis of encephalitis 22% were due to mumps virus, 20% to lymphocytic choriomeningitis, 20% to arthropod-borne viruses, 13% to herpes simplex, 5% to poliovirus, and 5% to other enteroviruses In this study an ætiological diagnosis was made in 81% of the cases of paralytic poliomyelitis 113 cases were due to poliovirus and 1 each to mumps, a Coxsackie B, and an Echo virus In Lennette's [5] study 24% of the vaccinated paralytic cases in which the ætiology was determined were due to poliovirus (the figure was 70% for the non-vaccinated), 17% were due to Coxsackie or Echo viruses, 5% to mumps virus, and 3% to herpes simplex Lennette et al [8] describe in detail 11 cases of mild paralytic "poliomyelitis" due to mumps virus All these patients recovered well, although 2 had mild residual weakness when examined two to five months after onset It is thus clear that mumps virus can cause encephalitis, lower-motor-neurone paralysis, and aseptic meningitis In Meyer et al's [7] study of the 71% of cases of aseptic meningitis in which an ætiological diagnosis was achieved about 23% were due to mumps virus and 13% to poliovirus McLean et al [9] in 1959–60 isolated mumps virus from the cerebrospinal fluid of 17 out of 42 patients with aseptic meningitis thought likely to be due to mumps In all, 56 cases were studied, and by virus isolation or serology 38 were shown to be due to mumps

It is now clear that several members of the enterovirus family besides poliovirus can occasionally cause mild paralytic poliomyelitis [10] Grist [11] has shown that in the Glasgow area in the summer of 1959 Coxsackie A7 caused a significant number of cases of paralytic poliomyelitis, including 1 death It seems certain that the relative frequency of these cases not due to poliovirus will increase in the next few years as the vaccination programme makes its impact felt In Northern Ireland Likar and Dane [12] have found that some cases suspected of being paralytic poliomyelitis are due to Russian spring-summer encephalitis or louping-ill virus

The ætiology of aseptic meningitis is varied and alters from year to year [13] Meyer et al [7] succeeded in making an ætiological diagnosis in 71% of cases, but the 45% of Lennette's [5] investigation is perhaps more representative of usual experience One reason for the relatively low recovery-rate of viruses in these cases may be that the methods of viral isolation are still inadequate despite all the recent improvements This is suggested by a study by Duncan [14] in which a new Echo virus (Frater), responsible for many cases of aseptic meningitis, was isolated much more frequently in human thyroid cells than in the more commonly used monkey-kidney or human amnion cells Grist [11] showed the importance of supplementing tissue-culture methods by the inoculation of suckling mice, since the Coxsackie A7 strains he studied did not grow in the commonly used tissue-culture cells Similarly, the high rate of ætiological diagnosis achieved by Meyer et al involved not only isolation of viruses but also a battery of serological tests on acute and convalescent sera to cover a wider range of possible ætiological agents Similarly, as McLean et al [9] showed, it is important to examine not only fæces but also cerebrospinal fluid if non-enteroviral viruses causing encephalitis, paralytic disease, or aseptic meningitis are to be recovered

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Dr G F ABERCROMBIE has been re-elected president of the College of General Practitioners

Dr N M GOODMAN, a principal medical officer of the Ministry of Health, has been appointed a deputy chief medical officer of the Ministry in succession to Dr G E Godber who, as already announced, becomes chief medical officer on Dec 1

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Special Articles

EYE SIGNS IN GRAVES' DISEASE

THE eye signs which accompany Graves' disease are so characteristic of the condition that it would be a great convenience if there was some form of standardised nomenclature with which to describe them Eponyms like Stellwag, von Graefe, and a host of others only add confusion and are often used to describe signs which their originators never intended The occasion of the Fourth International Goitre Conference, held in London in July, provided a unique opportunity for a group of people interested in eye signs to sit round a table and try to reach some agreement on classification

Sir Russell Brain took the chair, and the following were present

Dr Brown M Dobyns (Cleveland, Ohio), Prof Russell Fraser (London), Mr Keith Lyle (London), Prof James Howard Means (Boston), Dr Rulon W Rawson (New York), Mr Selwyn Taylor (London), and Dr Sidney C Werner (New York) Dr Nigel Oakley (London) acted as recorder

EXOPHTHALMOS, PROPTOSIS, OR EYE SIGNS

The word exophthalmos stems from the Greek and implies that the eye is out Proptosis is also Greek in origin and means that the eye is pulled forwards Ophthalmic surgeons have in the past used the word exophthalmos to imply an active protrusion and proptosis a passive one, the latter being due to an increase in the retrobulbar mass This is not a satisfactory distinction, nor is there a scientific basis for it

Exophthalmos (measured in millimetres of protrusion) appears to be the most satisfactory term which can be used to describe the disorder of the orbital contents in Graves' disease, but other changes, such as lid retraction, are not necessarily implied by it Exophthalmos is not, therefore, considered a completely satisfactory descriptive term It was agreed that the term " protrusio bulbæ " was superfluous

The possible alternative to using the above terms would be to refer to this phenomenon as " eye signs of Graves' disease " It must, however, be recognised that eye signs similar to those seen in Graves' disease may be seen in patients with Cushing's syndrome or even in patients with kidney disease, and one member made a strong plea for the term " endocrine ophthalmopathy " However, since the whole clinical picture may not be a single physiological entity, it seems best to adopt a purely descriptive nomenclature

PROGRESSIVE CHANGES

On turning to the natural history of exophthalmos it was considered that one of the important reasons for trying to document eye signs accurately was to predict future changes, even though this might be very difficult There was fairly general agreement on a number of specific points, among which were the following

Loss of visual acuity in Graves' disease rarely occurs without some degree of exophthalmos and never without increased retrobulbar pressure This loss falls into two separate categories (*a*) due to corneal ulceration and resulting corneal opacity, and (*b*) due to defects in the visual fields including paracentral or central scotomata, and these are due to pressure on the optic nerve or, possibly, circulatory disturbances

True lid-lag is virtually specific to hyperthyroidism and usually disappears on return to a euthyroid condition It may be due to increased tension in the levator palpebræ superioris

Even the most severe orbital lesions may show complete regression

Permanent impairment of function in the orbital contents is usually related to the duration and severity of the changes

CLASSIFICATION

When it comes to the classification of eye signs there were almost as many different classifications as there were people present However, there was general agreement that " malignant exophthalmos " (though a misleading term) referred to those cases in which protrusion continued to progress so that visual acuity was impaired and corneal ulceration or even loss of the eye appeared likely It was pointed out that lid retraction may, in some instances, be due to increased tension in the levator palpebræ superioris rather than to contraction of the unstriped muscle in the upper eyelid Such a mechanism should be carefully distinguished from the mechanical effect of mere protrusion of the eyeball on the upper lid

RECORDING OF EYE SIGNS

There was general agreement that eye signs should be carefully recorded and measured as far as possible, and one list, which most members took least objection to, had eight items as follows

1 Eyeball protrusion—measured from the lateral rim of the bony orbit

2 Lid retraction—measured at rest from the upper iris margin with the eyes looking horizontally forward

3 Lid-lag

4 Bulge of upper lid

5 Bulge of lower lid

6 Chemosis and peripheral conjunctival congestion—grades 1–4

7 Decreased resiliency of the eyeball estimated by pressure upon the closed eyelids

8 Impairment of ocular movements

When the abnormality cannot be directly measured it is useful to define different grades of severity, and a simple way of so doing is to give a number of plus signs, from + to ++++ It is then desirable that the same doctor always makes the assessment Better than this is to measure, where possible, as in 1 and 8

For eyeball protrusion different workers attach importance to a variety of methods The Hertel exophthalmometer was considered by most to be a valuable aid in measuring the degree of protrusion, but again it was stressed that the same observer must use the identical instrument when measuring progress in any one patient Accurate lateral photographs were also considered of value in assessing progress, and reference was made to an apparatus which fitted over the head and carried a mirror at the angle of the orbit together with a millimetre scale so that the eyes could be photographed showing the degree of protrusion and thus provide a permanent record The Copper orbitonometer was generally regarded as a most useful research tool, but is not suitable for general clinical application It does not appear to have yielded important information

CONCLUSION

Since we remain ignorant of the ætiology of Graves' disease it is not surprising that general agreement on nomenclature was not reached Some preferred the " eye signs of Graves' disease ", others were unwilling to drop " exophthalmos " while appreciating its limitations, one member preferred " endocrine ophthalmopathy " However, all agreed that the careful recording and grading of the eye changes, as described above, was of real value

SELWYN TAYLOR

The Widdicombe File

LXVII —ON BEING AN OMP

DEAR GURNEY,

I didn't get a chance to make my point properly the other night But, as you seemed openminded about Omps, I'm writing it down If it's true, as you said, that there's a shortage of ophthalmic consultants in the N H S, it could be important

Quite a lot of people, adequately qualified in ophthalmic medicine and surgery, earn the greater part of their living by carrying out refractions through the Supplementary Ophthalmic Services, and many of these Ophthalmic Medical Practitioners (O M P s) are also attached in some capacity to a hospital where they can do clinical work and surgery But some have no such hospital connection, and spend all their working days on the refraction of the eye—which (if they work hard enough) can in fact bring in quite a considerable income

Such a person to my way of thinking is properly designated an Omp Not for him the glamour of the keratoplasty, the doubts and sorrows of toiling, year in and year out, with a chronic uveitis, the rewarding glow attending the restoration of sight to someone in danger of losing it His placid life is ruffled by a minimum of responsibility, his success dependent upon an ability to carry out accurately the same procedures over and over again It is rather as though a lawyer, meticulously and completely qualified, elects or is condemned to spend his entire existence in the occupation of drawing up wills

But the Omp may have drifted into his vegetative existence faute-de-mieux rather than by design, and not so very long ago the Ophthalmic Group Committee said that all Omps should be encouraged to undertake some kind of work in the Hospital Eye Service The question is whether such work is available

To qualify for his " title ", an Omp needs to undergo a considerable training, and has to have both academic and practical experience in ophthalmology Indeed the qualifications of some Omps are at least equal to those of some of their more fortunate brothers who are classified as " consultants " It seems a pity therefore that their activities should be so severely circumscribed and restricted For they are permitted by law to carry out no form of treatment

Herein lies, to my way of thinking, a serious imperfection in the present scheme of things A patient attends a Medical Eye Centre, where an Omp does his work for the most part, because there he may be examined by a Medical Eye Specialist He often has, in addition to a possible refractive error, some comparatively trifling ophthalmic complaint, such as blepharitis, for which he wants advice He is, to say the least, puzzled when the specialist says in effect " you have a minor affection of your eyes which is easily amenable to treatment, but I am not permitted by law to advise you what to do about it—you must see your general practitioner about this, and he'll refer you to the hospital if he thinks it is necessary "

The patient's reaction to this may well be " What's the use of m attending a Medical Eye Centre at some distance from my home to see a Medical Eye Specialist if he can do no more than refer me to my G P to whom I could have gone in the first place ? I could just as well have gone to the sight-testing optician whose shop is just around the corner " And so the whole concept of the Medical Eye Centre, which is to encourage the public to have their eyes examined by an ophthalmic surgeon, falls flat on its face Of course I know the considerations which lie behind the strict limitation of the activities of the Omp, but the patient doesn't know about them, and his irritation at not getting the help he expects from the Medical Eye Specialist doesn't encourage him in future to have his eyes examined by such a person Which is a pity

On the other hand one reads and hears a good deal about overworked hospital outpatient departments, and in some cases delay in making appointments Here surely is a siding into which some of the routine and time-consuming work of the ophthalmic outpatients could reasonably be shunted ?

Take the case of the patient requiring periodic perimetry Such a case, diagnosed and properly referred by the Omp to the Hospital Eye Service, is not seen again by him certainly until a further refraction is indicated, and, if the refraction is later done at the hospital, perhaps never again This deprives the Omp of any further interest in the case But, the patient having been referred in the first place and the diagnosis confirmed, it would surely not be very difficult for him to be referred back to the Omp for routine perimetry and further observation? He can always be sent back to the hospital when the signs indicate this Yes, one knows that at present an Omp may not normally re-examine a case in less than a year, and one can hear the horrid word " abuse " rumbling off-stage, but if a consultant, *in referring a case back to an Omp for perimetry,* specifically states " this case requires examination every three months ", is this not a fair safeguard ? And it should not be impossible for ingenuity to cover other instances The additional cost involved, set against the Ben Nevis of Supplementary Ophthalmic Services expenses or the Everest of the N H S budget, would perhaps take on the dimensions of a sizable molehill—remembering that new glasses would not normally materialise from such " repeat visits "

As things are, I gather there's some doubt whether an Omp, seeing a patient suffering from, say, blepharitis, is entitled to give him a prescription for an appropriate remedy to be dispensed at his own expense, or even whether, strictly speaking, he is entitled to suggest to a general practitioner a course of action which would be likely to benefit a patient suffering from a complaint which could reasonably be treated by him Now that I am Omp 72 (retd) I hope I shan't get into a great deal of trouble if I confess to having transgressed in both respects with some frequency I feel that some patients were not ungrateful, and I can't believe much harm was done Whether the G P s concerned approved is not for me to say At least I had no complaints

In my opinion, therefore, the ability and potential of the Omp is not at present being utilised to the full, and the pressure on hospital outpatients could well be reduced by a redistribution of certain kinds of routine work There seems to be a sad tendency these days for people to say in shocked voice " Oh, but you can't do that, it isn't provided for in the Act " This has always made me feel that if the Act is demonstrably susceptible of improvement, then it is high time someone amended it I know of no other branch of Medicine in which a practitioner is for all practical purposes debarred from clinical work, and though the fruit at the top of the ophthalmological tree may still be as sweet as in former years, fewer students of moderate ability are likely to look for a place on the branches nearer the ground And to those who see in this an automatic selective mechanism, I would say that ophthalmology cannot thrive on selected material only for one thing there will not be enough of it, and for another in *all* branches of medicine useful work, and this includes clinical work, is done by the humbler members Such as

Yours sincerely,
O D LEA

Parliament

Penology in the Affluent Society

INTRODUCING the Criminal Justice Bill[1] in the House of Commons on Nov 17, Mr R A. BUTLER, the Home Secretary, admitted that he did so against a rather sombre background Last year, roughly a third of those convicted for indictable offences were between the ages of 14 and 21 and the total number of such offences known to the police was more than double that of 1958 No one method or one type of punishment would suffice to solve the problem of crime, but in his view some essentials must be tackled at once We must ensure that the police were brought up to strength and that their relations with the public were good We must expand the probation service to meet the increasing demands imposed by the high level of crime and the increasing responsibilities to be imposed by this new Bill We must remember the needs of the prison service He had appointed two bodies to examine the law The Criminal Law Revision Committee had already submitted a report on the law relating to suicide and attempted suicide, and were now considering larceny The Streatfeild Committee were considering the machinery of the superior courts Lord Ingleby's Committee had surveyed our system of juvenile courts and some of their recommendations had been fitted into the present Bill. Others, notably the proposal to raise the age of criminal responsibility, needed further consideration

A method of punishment which we have discarded is corporal punishment, and Mr Butler said that the Advisory Council on the Treatment of Offenders' report[2] confirmed the Government's judgment that it should not be reintroduced. He accepted the Council's view that the present powers of the courts for serious offences was adequate What was not adequate was the power to fine for less grave offences, and some proposals to this end, in respect of juveniles and their parents, were included in this Bill He added that he hoped soon to receive the report of the working party which was considering a scheme for compensating victims of crimes of violence

He recognised that the Bill would depend on the right buildings being available and the Prison Commission was driving ahead with the largest programme of building and refurbishing prisons that we have known for many generations 3 new open prisons had already been completed, 3 detention centres would be open in the next three months By the latter part of the year he hoped to have 10 detention centres in being, giving a total of 12 They were also planning to spend in the next few years about £5 million in the modernisation of the premises of approved schools It was intended to set up a small number of closed units, attached to existing schools, to provide for observation and treatment as well as secure custody Improved premises would be of limited value unless enough staff of the right calibre were attracted to the service and he had been struck by the difficulties arising from the general shortage of qualified social workers With the help of the Central Training Council in Child Care they were extending the training facilities for the staff of approved schools Improved salary scales had lately been agreed and they were seeking to improve the living conditions of residential staff

Reviewing the clauses of the Bill, Mr Butler described the provision for aftercare as one of its "most important and potentially beneficial proposals" Nothing we could do for a young man while he was in prison was of any value unless we could negotiate the readjustment to freedom successfully Extension of compulsory aftercare would create new problems of organisation and he was going to ask the Advisory Council to review existing practice The proposal in the Bill to amalgamate the Prison Commission and the Home Office was made because the original division of responsibility between the Commission as an executive authority and the Home Office as the policy-making body had disappeared It did not foreshadow any drastic change and it would not mean the dissolution of the Prison Board as a team of administrative and professional officials By this integration it might be possible to draw closer the prison and probation services and the approved school and borstal services Eventually he would like to see what was now the Prison Commission becoming part of a wider organisation covering all Home Office responsibilities for criminal justice and the treatment of offenders

Mr GORDON WALKER thought that the Bill made a little progress in the right direction but was inadequate to the tasks and crises facing the country Our research was still lamentably inadequate and our criminal statistics wholly misleading in many respects Sir KENNETH PICKTHORN did not accept the assumption that trying to reform was superior to trying to deter It was no good the Home Office getting more and more progressive if the result was an increase in crime The moral improvement of the criminal should be an indirect object The object of imprisonment should be the prevention of crime

Sir THOMAS MOORE found the Bill admirable, but suggested that it had a strange kinship with the 1948 Act with its insistence on more detention centres, more remand homes, and more and better prisons These, however, had not materialised, often with tragic results He knew of a boy of 16½ sent for two months to a prison for hardened criminals because there was no room in a borstal He was tempted to say that a good whipping would have done the bou less harm He was disappointed in the Advisory Council's report on corporal punishment He thought that the Council had relied too greatly on the Cadogan report of 1938 Since then the social and economic conditions of the country had improved Yet we had a gross and dramatic increase in deliquency and crimes of violence He asked the Home Secretary to consider giving the courts, for a trial period of five to ten years, the right to use the cane for criminals up to 17 years of age, and the birch for criminals of more than 17 The cat, with its implication of sadism, should be dropped, and he reminded the House that only the Home Office retained this form of punishment in its own prisons

Mr CLEMENT DAVIES pointed out that the Ingleby Committee had considered the problem in the early stages, not after the crime was committed, but when the child's mind might have been influenced In our primary schools he would like to see more attention paid by doctors to the mind rather than to body health If we gave more care to problem children in schools, he was sure there would be less delinquency

Mr CHRISTOPHER MAYHEW was one of the many speakers, who, unlike Sir Thomas Moore, accepted the Advisory Council conclusions Their report in Mr Mayhew's view had conclusively shown that corporal punishment made no difference one way or the other to the future career of a person who was punished. This linked with the important point raised earlier in the debate by Sir GEORGE BENSON, that whether an offender went to a borstal, prison, or a detention centre the evidence suggested that it had no effect on his career Whether an offender would go straight or not could be predicted with great accuracy from his family background, character, and previous career before he was sentenced If we accepted this disheartening conclusion, Mr MAYHEW suggested that the best penal system would be one which filtered out from the rest those who would go straight anyway They should be released as quickly as possible, and the others shut up, humanely and productively, for a long time Turning to the offender's social background, he said that our affluent society might have been designed to aggravate and exploit any weakness of personality

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[1] See *Lancet* Nov 12 1960 p 1082
[2] See *ibid* Nov 19 1960 p 1149

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The patient's reaction to this may well be " What's the use of my attending a Medical Eye Centre at some distance from my home to see a Medical Eye Specialist if he can do no more than refer me to my G.P. to whom I could have gone in the first place? I could just as well have gone to the sight-testing optician whose shop is just around the corner." And so the whole concept of the Medical Eye Centre, which is to encourage the public to have their eyes examined by an ophthalmic surgeon, falls flat on its face. Of course I know the considerations which lie behind the strict limitation of the activities of the Omp, but the patient doesn't know about them, and his irritation at not getting the help he expects from the Medical Eye Specialist doesn't encourage him in future to have his eyes examined by such a person. Which is a pity.

On the other hand one reads and hears a good deal about overworked hospital outpatient departments, and in some cases delay in making appointments. Here surely is a siding into which some of the routine and time-consuming work of the ophthalmic outpatients could reasonably be shunted?

Take the case of the patient requiring periodic perimetry. Such a case, diagnosed and properly referred by the Omp to the Hospital Eye Service, is not seen again by him certainly until a further refraction is indicated, and, if the refraction is later done at the hospital, perhaps never again. This deprives the Omp of any further interest in the case. But, the patient having been referred in the first place and the diagnosis confirmed, it would surely not be very difficult for him to be referred back to the Omp for routine perimetry and further observation? He can always be sent back to the hospital when the signs indicate this. Yes, one knows that at present an Omp may not normally re-examine a case in less than a year, and one can hear the horrid word " abuse " rumbling off-stage, but if a consultant, in referring a case back to an Omp for perimetry, specifically states " this case requires examination every three months ", is this not a fair safeguard? And it should not be impossible for ingenuity to cover other instances. The additional cost involved, set against the Ben Nevis of Supplementary Ophthalmic Services expenses or the Everest of the N.H.S. budget, would perhaps take on the dimensions of a sizable molehill—remembering that new glasses would not normally materialise from such " repeat visits ".

As things are, I gather there's some doubt whether an Omp, seeing a patient suffering from, say, blepharitis, is entitled to give him a prescription for an appropriate remedy to be dispensed at his own expense, or even whether, strictly speaking, he is entitled to suggest to a general practitioner a course of action which would be likely to benefit a patient suffering from a complaint which could reasonably be treated by him. Now that I am Omp 72 (retd.) I hope I shan't get into a great deal of trouble if I confess to having transgressed in both respects with some frequency. I feel that some patients were not ungrateful, and I can't believe much harm was done. Whether the G.P.s concerned approved is not for me to say. At least I had no complaints.

In my opinion, therefore, the ability and potential of the Omp is not at present being utilised to the full, and the pressure on hospital outpatients could well be reduced by a redistribution of certain kinds of routine work. There seems to be a sad tendency these days for people to say in shocked voice " Oh, but you can't do that, it isn't provided for in the Act." This has always made me feel that if the Act is demonstrably susceptible of improvement, then it is high time someone amended it. I know of no other branch of Medicine in which a practitioner is for all practical purposes debarred from clinical work, and though the fruit at the top of the ophthalmological tree may still be as sweet as in former years, fewer students of moderate ability are likely to look for a place on the branches nearer the ground. And to those who see in this an automatic selective mechanism, I would say that ophthalmology cannot thrive on selected material only for one thing there will not be enough of it, and for another in *all* branches of medicine useful work, and this includes clinical work, is done by the humbler members Such as

Yours sincerely,
O D Lea

Parliament

Penology in the Affluent Society

Introducing the Criminal Justice Bill[1] in the House of Commons on Nov 17, Mr R A Butler, the Home Secretary, admitted that he did so against a rather sombre background Last year, roughly a third of those convicted for indictable offences were between the ages of 14 and 21 and the total number of such offences known to the police was more than double that of 1958 No one method or one type of punishment would suffice to solve the problem of crime, but in his view some essentials must be tackled at once We must ensure that the police were brought up to strength and that their relations with the public were good We must expand the probation service to meet the increasing demands imposed by the high level of crime and the increasing responsibilities to be imposed by this new Bill We must remember the needs of the prison service He had appointed two bodies to examine the law The Criminal Law Revision Committee had already submitted a report on the law relating to suicide and attempted suicide, and were now considering larceny The Streatfeild Committee were considering the machinery of the superior courts Lord Ingleby's Committee had surveyed our system of juvenile courts and some of their recommendations had been fitted into the present Bill Others, notably the proposal to raise the age of criminal responsibility, needed further consideration

A method of punishment which we have discarded is corporal punishment, and Mr Butler said that the Advisory Council on the Treatment of Offenders' report[2] confirmed the Government's judgment that it should not be reintroduced He accepted the Council's view that the present powers of the courts for serious offences was adequate What was not adequate was the power to fine for less grave offences, and some proposals to this end, in respect of juveniles and their parents, were included in this Bill He added that he hoped soon to receive the report of the working party which was considering a scheme for compensating victims of crimes of violence

He recognised that the Bill would depend on the right buildings being available and the Prison Commission was driving ahead with the largest programme of building and refurbishing prisons that we have known for many generations 3 new open prisons had already been completed, 3 detention centres would be open in the next three months By the latter part of the year he hoped to have 10 detention centres in being, giving a total of 12 They were also planning to spend in the next few years about £5 million in the modernisation of the premises of approved schools It was intended to set up a small number of closed units, attached to existing schools, to provide for observation and treatment as well as secure custody Improved premises would be of limited value unless enough staff of the right calibre were attracted to the service and he had been struck by the difficulties arising from the general shortage of qualified social workers With the help of the Central Training Council in Child Care they were extending the training facilities for the staff of approved schools Improved salary scales had lately been agreed and they were seeking to improve the living conditions of residential staff

Reviewing the clauses of the Bill, Mr Butler described the provision for aftercare as one of its " most important and potentially beneficial proposals " Nothing we could do for a young man while he was in prison was of any value unless we could negotiate the readjustment to freedom successfully Extension of compulsory aftercare would create new problems of organisation and he was going to ask the Advisory Council to review existing practice The proposal in the Bill to amalgamate the Prison Commission and the Home Office was made because the original division of responsibility between the Commission as an executive authority and the Home Office as the policy-making body had disappeared It did not foreshadow any drastic change and it would not mean the dissolution of the Prison Board as a team of administrative and professional officials By this integration it might be possible to draw closer the prison and probation services and the approved school and borstal services Eventually he would like to see what was now the Prison Commission becoming part of a wider organisation covering all Home Office responsibilities for criminal justice and the treatment of offenders

Mr Gordon Walker thought that the Bill made a little progress in the right direction but was inadequate to the tasks and crises facing the country Our research was still lamentably inadequate and our criminal statistics wholly misleading in many respects Sir Kenneth Pickthorn did not accept the assumption that trying to reform was superior to trying to deter It was no good the Home Office getting more and more progressive if the result was an increase in crime The moral improvement of the criminal should be an indirect object The object of imprisonment should be the prevention of crime

Sir Thomas Moore found the Bill admirable, but suggested that it had a strange kinship with the 1948 Act with its insistence on more detention centres, more remand homes, and more and better prisons These, however, had not materialised, often with tragic results He knew of a boy of $16^{1}/_{2}$ sent for two months to a prison for hardened criminals because there was no room in a borstal He was tempted to say that a good whipping would have done the bou less harm He was disappointed in the Advisory Council's report on corporal punishment He thought that the Council had relied too greatly on the Cadogan report of 1938 Since then the social and economic conditions of the country had improved Yet we had a gross and dramatic increase in deliquency and crimes of violence He asked the Home Secretary to consider giving the courts, for a trial period of five to ten years, the right to use the cane for criminals up to 17 years of age, and the birch for criminals of more than 17 The cat, with its implication of sadism, should be dropped, and he reminded the House that only the Home Office retained this form of punishment in its own prisons

Mr Clement Davies pointed out that the Ingleby Committee had considered the problem in the early stages, not after the crime was committed, but when the child's mind might have been influenced In our primary schools he would like to see more attention paid by doctors to the mind rather than to body health If we gave more care to problem children in schools, he was sure there would be less delinquency

Mr Christopher Mayhew was one of the many speakers, who, unlike Sir Thomas Moore, accepted the Advisory Council conclusions Their report in Mr Mayhew's view had conclusively shown that corporal punishment made no difference one way or the other to the future career of a person who was punished This linked with the important point raised earlier in the debate by Sir George Benson, that whether an offender went to a borstal, prison, or a detention centre the evidence suggested that it had no effect on his career Whether an offender would go straight or not could be predicted with great accuracy from his family background, character, and previous career before he was sentenced If we accepted this disheartening conclusion, Mr Mayhew suggested that the best penal system would be one which filtered out from the rest those who would go straight anyway They should be released as quickly as possible, and the others shut up, humanely and productively, for a long time Turning to the offender's social background, he said that our affluent society might have been designed to aggravate and exploit any weakness of personality

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[1] See *Lancet* Nov 12, 1960, p 1082
[2] See *ibid* Nov 19, 1960 p 1149

It stressed ambition, success, and wealth It brought strong pressure on young people, through advertising and salesmanship, to spend freely on cigarettes, clothes, drinks, and all the rest of it It repeatedly offered something for nothing as in premium bonds or pools Our newspapers, films, and television too often glamorised crime for our amusement and entertainment It had been said that "a society gets the crime it deserves" He believed that was true of our overcommercialised affluent society

Mr W F DEEDES pointed out that the detention centres of the future would have enlarged functions, and he thought that the administrative consequences were being taken a little lightly The existing centres were staffed by volunteers from the prison service Would it be possible to get volunteers for the ten new centres? The centres would be receiving an increasingly mixed bag of offenders We must recognise that among juvenile delinquents today there was a hard core of thoroughly vicious, amoral, dangerous youngsters If the detention centre was to be the civilised alternative to the birch, it must be not simply an instrument for the reclamation of misguided youth It must also be the principal means of protecting society against violence which was often rendered more beastly, thoughtless, and dangerous by the immaturity of the attacker Mr T L IREMONGER had found quite a few psychopaths in approved schools and borstals He suggested that those should be weeded out and given separate treatment for the sake of the staff and the rest of the school The Mental Health Act might be used to detain them for treatment

Sir REGINALD MANNINGHAM-BULLER, the Attorney-General, in summing up the debate, said that one of the main reasons why he had supported the retention of the birch in 1948 was to avoid sending young offenders to prison When this Bill came into effect it would mean that young offenders would not ordinarily be sent to prison and the main argument for judicial corporal punishment would fall to the ground The rate of crime in 1959 among males in the age-group 15 to 17 was almost twice the 1954 figure, and he could not have supported this Bill unless he was satisfied that it was in no sense a soft Bill In fact it provided a more strenuous and rigorous regime for young offenders than they would have to undergo in a local prison It was against this background that any proposals for the reintroduction of corporal punishment must be considered and he did not think that it would be right or wise to treat lightly the conclusion which the Advisory Council had reached unanimously after hearing a mass of evidence from people of varying views

Parliamentary Medical Committee

The following have been elected as officers of this all-party committee Sir Malcolm Stoddart-Scott (chairman), Dr J Dickson Mabon (hon secretary), and Dr Donald Johnson (hon treasurer)

QUESTION TIME

Diesel Fumes

Mr N N DODDS asked the Minister of Health, as representing the Minister of Science, if he would give details of the experiments carried out on behalf of his department which show that diesel fumes are not endangering health —Mr ENOCH POWELL replied Investigations into the effects on health of diesel exhaust fumes form part of the programme of research on air pollution undertaken by the Medical Research Council They have included statistical studies on a large group of patients with lung cancer, which showed that in this group there was no greater proportion of persons who might have been expected from the nature of their employment to have greater exposure to vehicle exhaust fumes, and a study on London Transport employees, in collaboration with the chief medical officer of London Transport, which provided no evidence of significantly greater mortality from lung cancer among men working in diesel-bus garages Analyses of the air in bus garages and busy streets have shown that motor exhaust fumes are only one of many pollutants and that their content of benzpyrene, a known cancer-producing agent, is very small in relation to the total amount in the atmosphere from all sources Even in congested spaces, such as vehicular tunnels, pollution from exhaust fumes has been found to be no greater than the pollution of an urban atmosphere by coal smoke on many winter evenings It seems reasonable, therefore, to deduce from these findings that diesel fumes are not endangering health

Manufacturing Expenses

Mr KENNETH ROBINSON asked the Minister of Health whether he was aware that drug manufacturers included in their manufacturing expenses such promotion expenses as continental holidays offered as prizes to pharmacists, and to what extent he took into account such expenses in approving the costs of new drugs prescribed within the National Health Service —Mr POWELL replied I am aware of one recent instance of this, but am told that the firm concerned does not intend to use this type of sales promotion in future The costs of new drugs prescribed within the National Health Service are not subject to my approval Mr ROBINSON Does not the Minister agree that this type of advertising, which was indulged in by Aspro-Nicholas in trying to introduce a new antibiotic, can only reflect adversely on the pharmaceutical industry as a whole? Will he do everything in his power, by persuasion, to see that it does not happen again?—Mr POWELL Yes

Group Practice Loans

Mr L A PAVITT asked the Minister why the average time for approving loans to group practices was 4½ months, and if he would take steps to shorten this period —Mr POWELL The committee needs this time to study the proposed arrangements and plans, to visit the groups, and to get agreement to any modifications necessary

Mr PAVITT asked the Minister what was the maximum loan granted per doctor in a group practice receiving loans from the fund established for that purpose —Mr POWELL £2500

Drugs and Dressings for Private Patients

On a rough estimate, the extra annual cost of providing drugs and dressings on National Health Service terms for residents in Britain not now registered with an N H S doctor might be between £2 million and £3 million

Hospital Development Unit

This Ministry of Health unit comprises 13 full-time and 8 part-time professional officers The function of the unit is to ensure that the most up-to-date knowledge and experience is assembled and brought to bear on all aspects of hospital building It has published a bulletin on operating-theatre suites and is preparing for publication further bulletins on specific departments, in addition to some 30 building notes on the features and standards which should be embodied in the design of modern hospitals It will itself be responsible for an out-patient department and kitchen which are to be built as development projects

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Medicine and the Law

Anæmia Due to Potassium Perchlorate ?

AT a Southend inquest on Nov 15, an open verdict was returned on a 29-year-old woman who died after treatment of a thyroid condition with potassium perchlorate [1]

A senior medical registrar said in evidence that treatment with this drug had been begun in June The thyroid symptoms were relieved, but by Sept 29 the patient was extremely anæmic There is no previous record of this drug producing the failure There have been reports where white blood cells have not been produced as a result of the drug but these patients all recovered'

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[1] *Times*, Nov 16 1960

In England Now

A Running Commentary by Peripatetic Correspondents

THERE was a time (it seems odd to think of it now) when we knew very little about libraries We began our official career as a custodian of books some years ago, as a member of the Preclinical Library Committee, recommending books in a carefree way and adopting a proprietorial air over the journal racks when we visited our domain By diligent attention to detail we rapidly climbed the ladder of promotion to the post of Chairman, and in counsel with our studious and reliable Preclinical Librarian we developed such striking lines of policy as the provision of red linoleum for the floor and the planting of flame-trees outside the windows to keep the sun off We even asked the university for an air-conditioning unit so that the students might read without the risk of heat exhaustion Naturally, subversive notions of this kind could not be tolerated in any respectable university, and we awoke one morning to find that we had been kicked upstairs into membership of the University Library Committee itself This body operates on an altogether more rarefied plane, meeting in the Vice-Chancellor's room and fortifying itself with tea and chocolate biscuits

After our translation we made a general tour of the University Library to examine the ramifications of our new responsibility We prowled at will through the forbidden hinterland, entering the reference staff-room, the cataloguing staff-room, the orders room, and the acquisitions department We visited the bindery, the photographic room, and the book-lift A chat on logistics with our learned and genial Librarian revealed to us that each undergraduate reader required 25 sq ft of space, and each postgraduate 35 sq ft, that the accepted ratio of seats to full-time students is 1 3, and that the standard height of book stacks is 7 ft 6 in The whole atmosphere was quiet and scholarly, far removed from that of our early struggles in the Preclinical Library

Finally we visited the reading-rooms The books did not frighten us so much—after all, we had been nipping in and out to borrow Trollope for years, and it had not escaped our notice that there were other sorts of books around—it was the journals which pointed up our narrow-minded professional outlook In agriculture, for example, it seems that they read *Beef Situation* and *Herbage Abstracts* The chemists receive, among others, the *Perfumery and Essential Oil Record*, and *Pipe Roll Society* is required reading for lawyers In education they spend happy hours reading *Let's Dance*, or, more soberly, *Laban Art of Movement*, and, for a dreamy mood, the enigmatic *Etude* The zoologists are addicted to *Insects Sociaux* and *Tuatara*, and the psychologists find instruction as well as relaxation in studying the *Journal of Projective Technique* The engineers—solid earthy creatures—while away their long weekends with *Beama, Diesel Engine Users' Association*, and *Muck Shifter*

At the next meeting of the Library Committee I am going to suggest that some of these journals should be routed through the Preclinical Library to broaden, for the medical student, the straitened educational experience which we all so much deplore It is safe to say that no-one could read *Muck Shifter* and remain unbroadened, and a study of *Beef Situation* could only expand the restricted technical horizon In return we could offer the Faculty of Arts a choice of *Brain* or *Gut*, and the Faculty of Education might like to glance through a few recent issues of *Blood*

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One of my quirks is to write down, in a big exercise book, what I think of each book I read I have just been looking back at what I recorded twenty years ago about *Lady Chatterley's Lover* when I read it at the age of twenty-five

'I think it's a good book—not by any means pornography I think it's a good story and I think the message of the coming downfall of industrial civilisation unless we have more tenderness is a very feasible idea But I don't like the coldness of it—it's very hard and bare—there's no happiness in the book but there was no happiness in Lawrence's heart when he wrote it I liked it better than *Sons and Lovers*, but they share this barren chilliness that's so dispiriting Strangely enough, both books are also at times highly romantic and the descriptions of the countryside and the flora and fauna are almost lyrical He was a queer mixture more of a poet than anything else, in the sense of temperament There are one or two surprising bits of good characterization and action-story-telling in this book as, for instance, the time that Clifford's chair wouldn't go up the hill

I had forgotten all about the incident of Clifford's chair, but I suppose the remarkable thing about these comments is that they include no mention of four-letter words It looks as though their presence made no great impact upon me

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My happiest memories of that pharmaceutical feast, the London Medical Exhibition, go back to 1946 As a first-year preclinical student I had borrowed my father's invitation It lent me a spurious eminence and opened every door, and I even ended up with a free tea Still, even this year, over the second stall of this decorous and decorated market-place I met my tennis partner of ten years ago, and we had exactly the right amount of time to catch up with our news Round the corner behind a cardiograph or something, the size of a house, meandered my first medical superintendent—long since abolished poor man At this point it struck me that the exhibition should stimulate the reunion aspect Perhaps the prospectus could allot days and times so that the old boys of St Cecil's, say, would know there was the most chance of seeing old pals at 3 30 on Tuesday

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The undertaker's clerk and I met over a cremation form The new crematorium, it appeared, had been open for over two months " Oh yes, it's doing very well, I believe—and fancy *you* not knowing it was open all this time, doctor "

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A difficult problem in human rights was raised last year by a call from the local vet, whose practice covers one of the remoter valleys of our western fringe, a valley where Government had early insisted that all cattle should be healthy Within the last few months, he declared, 14 fine Friesians had become violently tuberculin-positive, and had therefore gone the way of all flesh at great expense to the taxpayer, did I know anything, he asked, about Farmer Cobbleigh, who looked very unwell, and would I please take any necessary steps ?

This local notable's records showed that he had indeed been treated some years before with antibacterial agents for a large pleural effusion, but had absconded and stoutly refused our further attentions Ignobly, I asked the health visitor to call on him, but she found the portcullis firmly down His family doctor went into the assault next, but was met with abuse and showers of stones (well aimed from the spinning gallery) Finally, the senior partner from the next valley donned a tin hat, and took the place by storm in his Landrover, after which he carried Cobbleigh in triumph directly to the hospital His chest radiograph showed galloping consumption of such exuberant quality that no normal lung was to be seen Now, after a year in hospital, he is no longer infectious, and less breathless and more robust than most people, and he has perhaps wisely obtained work as a clerk

There was no further epidemiological problem, for he had no human contacts at all, in fact he had done all the milking himself for years for this very reason

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I have had a scooter, of one kind or another, for some years, but until lately I did not feel it belonged with my colleagues' motor-cars I used to park it a little way from the main entrance, and I always removed my crash helmet before I went inside the hospital But now at last, the scooter has been accepted as a means of transport for the medical profession In the paper the other day I read the headline Drugs Stolen from Doctor's Scooter "

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In a transatlantic journal I came across a report on " Salmonellosis spread by a dietary supplement of Avian Source ' Pate de foie gras was my first guess, or could it be larks' tongues ? No—egg nog

Letters to the Editor

TUMOURS OF THE BLADDER

SIR,—In your leading article of Nov 12 you make the comment " In the past decade the causes, treatment, and prevention of bladder tumours have aroused much interest Fascinating questions surround the incidence of this disease Why is it increasing in younger males? Why is it apparently commoner in towns than in the country? Why is it rare in Japan and India? Now that β-naphthylamine is no longer employed in the dye, chemical, or rubber industry, which industries still use carcinogens such as benzidine ?"

In my opinion it is high time indeed that honest, unequivocal, and comprehensive answers were openly given to questions like the last In fact, for reasons set out below, the question does not go far enough It should be extended to cover all the recognised bladder carcinogens and should relate to past as well as present usage

Part of the mortality from tumours of the bladder in this country is unquestionably due to occupational factors The results of using the chemical agents so far known to be carcinogenic have taken a long time to become manifest Some of the substances concerned are no longer in common industrial use, and others are used with much more protection of workers than in the past, but the effects, already determined before these changes took place, will continue to show for years yet to come

It follows that an epidemiologist is precluded from answering a vital question, posed below, unless he has a knowledge of what known carcinogens have been used, in what processes they were employed, in what parts of the country these processes were carried out, and between what dates they were operated

The vital question facing the epidemiologist is this

Taking into account our knowledge of the epidemiology of bladder cancer resulting from exposure to known carcinogens in the dyestuff manufacturing industry [1] and our much less detailed knowledge of bladder cancer resulting from exposure to certain antioxidants in the rubber manufacturing industry,[2] can we say that the present mortality pattern from bladder cancer within the country is compatible with the hypothesis that all the major industrial bladder carcinogens have been identified and the hazards resulting from them acceptably mitigated?

Side by side with this problem of social medicine is the medical practitioner's concern with the individual patient and his dependants A statutory instrument [3] prescribes for benefit under the National Insurance Act tumours of the urinary bladder which occur in workers in insurable occupations who have been, in the course of their work, exposed to certain named substances at any time after July 4, 1948 The industrial processes where this may occur are often such that the worker operating them is unlikely to know the chemical nature of the substances he uses Many medical practitioners feel it is their duty to give advice as to when a claim under the Act would be justifiable, but they are unable to do so because of the absence of published information about the industrial uses of the substances concerned

There may be ways whereby members of the public can obtain this information which, to be useful, must be free from the restriction of confidentiality If so, I have been unable to discover them In unsuccessful attempts to do so in the past I have drafted questions for a Member of Parliament to lay before the House and have put the same questions to an appropriate official of the Factory Department

One author seems to have been more successful, for a categorical statement that benzidine has in the past been used in the rubber industry and that its use has now been abandoned has recently been published [4] Unfortunately no information about how or where the material was used, the date when usage ceased, or the source of the information was given

May I use the authority of your columns, Sir, to urge that an independent person or body is given the facilities to compile and publish a reliable history of the industrial use of the known bladder carcinogens? Without this information some of the " fascinating questions " you mention can never be answered, and without it medical men cannot give adequate advice to patients who might be entitled to industrial injury benefit

London, S W 5 R A M CASE

MODERN CLINICAL BIOCHEMISTRY

SIR,—Is it not true that the only justification for our professional existence is the benefit to the patient? If we admit this, the studied self-worship of the ultra-specialist and that of the lonely egocentric on the peak of his pyramid of subordinates, alike appear ridiculous The problem at the centre of this correspondence becomes much simpler how can we provide patients with the widest range of laboratory care, taking due note of the frequency with which different types of laboratory assistance are needed, the readiness with which the patient can be brought to hospital, and the availability of specialists of various kinds

In large cities patients can be moved by ambulance quickly and smoothly, and distances are such that few suffer injury by a journey across the city In cities, therefore, we need few hospitals, but each must be large and carry a staff which includes most specialties In city hospitals we therefore need specialists in all four branches of laboratory medicine—pathology *sensu Anglicano*, a fourth meaning for Dr Hendry (Nov 19)—but they should be ready and able to exchange their views on any matter which may concern the patient directly or indirectly (for example, the bacteriologist, as hygiene officer, may have to forbid the entrance to the wards of a biochemical technician suffering from a boil) It is therefore desirable that departmental heads be on terms of amity rather than enmity, and that each should have some acquaintance with the work of the others, even though this acquaintance be superficial, such as that acquired by a registrar who spends only 6 months in a department

In many country areas a hospital with 200–300 acute beds may have to serve the needs of a small town and a large and sparsely populated rural district Such a hospital is necessarily staffed mainly by general physicians and surgeons, and it is unreasonable to provide a full staff of laboratory specialists who would be unable to obtain enough material to foster their especial skills However, in such centres the patients who need really esoteric investigation are rarely acutely ill, and can usually be transferred to a larger centre Such hospitals need a general pathologist who knows something about all branches, but more about one or two My experience is that for every patient who needs a complex series of chemical investigations done within a few hours, ten need blood-transfusion, and a hundred need bacteriological or hæmatological investigation, with rare exceptions histopathological investigations could be carried on some miles away It seems to me that the pathologist attached to such a hospital needs to be a very well-trained bacteriologist, to know quite a lot about blood transfusion and hæmatology, and to have some knowledge of clinical chemistry—last because lack of it is likely to kill fewer patients than lack of the other skills

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[1] Papilloma of the Bladder in the Chemical Industry a study of its cause and prevention Association of British Chemical Manufacturers London 1953

[2] Case R A M Hosker M E *Brit J prev soc Med* 1954 8 39

[3] S I no 1740 1953

[4] Poole Wilson D S *Proc R Soc Med* 1960, 53 813

The function of the pathologist in his hospital will also vary according to the time spent in hospital by consultant clinicians The diagnostic acumen of Dr Osborn (Nov 5) would hardly be required if his clinical colleagues spent most of their working time inside the hospital—and it can hardly be exercised on many of the patients who occupy the 2000-odd beds for which he is reputed to be pathologically responsible without his being absent from his laboratories for most of the working day If physicians are rarely in the hospital, the pathologist usually takes their place—often willingly—but I doubt whether the substitution is for the good of the patient

There is no doubt that there are about 200 centres in which a biochemist or chemical pathologist is needed, and which is appointed will depend on various committees' appreciation of local needs For my part, I believe that the best solution would be to recruit 1st-class or 2nd-class honours graduates in chemistry and pay them a salary while they undertake their medical studies, and complete not only their intern year but also 2 years as registrar in general pathology (*sensu Anglicano*), so that they will have that acquaintance with their colleagues' specialties which will enable them to cooperate fruitfully

However, there are at least as many centres in which the general pathologist is inevitable, at least for a generation, and I submit that since (1) every medical graduate has learnt some chemistry, (2) pathologists *sensu Anglicano* are highly selected, and (3) embryo pathologists who wish to learn more chemistry are even less common, it seems not to be excluded that the registrars selected for an extra year's work in chemistry may acquire quite a useful knowledge, and might even be stimulated to go on learning

There is no reason for medically qualified biochemists to avoid the hospital service, for there are consultant posts, and I believe more would appear were the money available slightly increased and the supply of qualified persons larger But I have great sympathy with the non-medical biochemists in their difficulties outlined by Dr Woolf (Nov 12) and confirmed by Mr Love (Nov 19) Hospital administrators, medical or lay, seldom realise that the professional future of the non-medical biochemist depends almost entirely on the original work he can undertake, and I am sorry to hear that he still suffers the mixture of suspicion and patronage which I noted 20 years ago among junior medical, nursing, and administrative staff—but which was so strikingly absent from my senior medical colleagues, to whom I still feel a sense of indebtedness and gratitude I do not know how these problems can be resolved—perhaps by educating our administrators—but I see no advantage in making non-medical biochemists the only advisers on clinical chemistry to the regional boards, when there are doubly-qualified men who are at least as suitable for this duty

London, N W 10 GEORGE DISCOMBE

THE FEMALE PROSTATE

SIR,—Mr Rhodes (Oct 15) asks what I meant to convey by approving (Oct 1) Mr Moore's statement[1] that " It is unfortunately still traditional for urinary symptoms in the female to lead to a gynæcological consultation " The answer is that in my opinion urinary complaints in female (or male) should be treated by those specially trained in urology, just as patients with gynæcological symptoms should be seen and treated by those trained in gynæcology

Mr Rhodes further says " the relationships between gynæcologists and urologists are such that they each need the other at times " I agree entirely, but why limit these relationships to the two specialties only? Surely this applies to all of them

As to backbiting, &c, would a proctologist be high-horse-riding if *he* and not a gynæcologist saw and treated postpartum hæmorrhoids? It is to be hoped that Mr Rhodes's choice of words (" backbiting and high horse ") is merely his personal manifestation of the truth of the old Talmudic saying " Rivalry of Authors enriches Wisdom " (*Baba Bathra*, 21, p 1)

Tel Aviv HERZL KOOK

THE BORDERLINE FOR SEVERE SUBNORMALITY

SIR,—As Dr MacMahon and Dr Clarke (Oct 29) pointed out, it will be unfortunate if, at a time when great changes are taking place in the mental-deficiency services in this country, we now abandon any serious attempt to classify the mentally subnormal by *grade* of mental defect The term " severe subnormality " seems likely to be applied to patients whose condition varies from profound idiocy to the milder grades of feeble-mindedness This may, as your correspondents say, have regrettable implications for clinical practice It will also mean the end of much serious epidemiological research—just at a time when it is beginning to produce fruitful results Not only will it be impossible to compare our experience in the future with what it was in the past, but we shall be unable to relate what is happening in England and Wales to what is happening in other countries dealing with similar problems Again, the new terminology cuts right across the educational criteria of mental subnormality, by lumping together those educationally subnormal persons who later come to be in need of care with the lower-grade defectives who in childhood are excluded from the educational system Prospective studies will thus be difficult to carry out

Perhaps the best way out of the difficulties likely to arise from the new terminology would be to insist that for statistical and record purposes the terms " subnormal " and " severely subnormal " are always qualified by an I Q rating If possible such ratings should be based on scores obtained on properly administered intelligence tests But even a clinical judgment, expressed in deciles (I Q 40–49, 60–70, &c) would be better than nothing

The value of I Q s for statistical purposes is extremely great, as can be easily demonstrated

(1) Whereas perhaps only 10% or fewer of adults with I Q s of less than 50 are able to be employed on the open market, at least 80% of those with I Q s of over 50 are fully employable

(2) The cut-off point for employability, as for educability and marriageability, is 50+ rather than 60 or 70, as has been shown by Ferguson in his studies of Glasgow school-leavers, as well as by many others

(3) Even within the imbecile grade there is a sharp gradient of educability A recent American study by Goldstein of the " lower limits of eligibility for classes for trainable (i e, imbecile) children " showed that the I Q was the most important single determinant of educability in the training centre 15 out of 16 children with I Q s below 25 (94%) were excluded from the training centres during the course of his investigation Only 6 of the 55 children (11%) with I Q s between 25 and 34 and 1 out of 45 children (2%) with I Q s over 35 were so excluded Neither clinical diagnosis, mental age, nor Vineland social maturity score had such discriminatory power

(4) There are immense differences between idiots and imbeciles in the management problems they present, and in expectation of life Staff requirements and institutional accommodation for the various grades are very different, as is the average time that high-grade and low-grade patients require institutional care

For all its shortcomings—many of which are well-recognised by psychologists who have been indefatigable in drawing attention to them in recent years—the I Q remains one of the most powerful diagnostic tools we have in psychiatry and in education If we are to give up the traditional grading of mental defect, as it seems we must, let us hang on to intelligence quotients until something better turns up to replace them

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[1] *Lancet*, 1960 i 1305

Institute of Psychiatry,
Maudsley Hospital,
London, S E 5

J TIZARD

"WHAT IS WRONG WITH ME?"

SIR,—Nearly every patient who feels ill or has some symptom says to himself or herself " I wonder what is the matter with me ? " Frequently they ask their family doctor, who possibly replies " Oh, it is only a bit of flu," or a " touch of catarrh " or " rheumatism ", and the patient is satisfied

If, however, the patient is sent to the hospital, the position is very different The patient still asks himself " what is the matter with me ? " but very seldom has the courage to ask anybody The atmosphere here seems to be that of the old nurseries, " ask no questions and you will hear no lies " How often one hears a patient just out of hospital, to whom one makes sympathetic noises, and asks what was the trouble, say, " Oh I don't know, they never tell you anything in hospital " Many of these patients go on worrying, particularly if they suspect rightly or wrongly that the condition was cancer One patient in hospital the other day said to a visitor, " I know I have cancer but they won't tell me," and then, turning to the ward sister, said " why won't you confirm it ? " The sister is reported to have replied, " The nurses are not allowed to discuss ailments with the patients " That may or may not be a good rule, but it should be the duty of *someone*, houseman or registrar, to tell *every patient* in lay language before leaving hospital what was wrong with him or her This is an important part of the treatment

Very seldom will a " white lie " have to be told, but if it is the " lie " should be passed on to the G P

" Knowledge is the antidote to Fear "—Emerson

MALCOLM DONALDSON
Honorary Secretary,
Cancer Information Association

Oxford

AGRANULOCYTOSIS ASSOCIATED WITH IMIPRAMINE

SIR,—Imipramine has come to be regarded as a valuable drug in the treatment of depression Side-effects have not been unduly troublesome but agranulocytosis has been reported twice [1 2] A patient recently treated with imipramine at the Maudsley Hospital developed agranulocytosis from which she recovered

A woman of 70 was admitted to the Maudsley Day Hospital on May 17, 1960, with a depressive illness Treatment with imipramine ('Tofranil', 25 mg b d) was started on May 19, and she was also given 0 1 g quinalbarbitone at night occasionally, as required Four days later nausea and dizziness developed with a temperature of 99 4°F , for which no cause could be found The blood-count at that time was entirely normal Imipramine was stopped on May 27, but as the symptoms continued she was admitted to the ward under the care of Dr Felix Post, where they gradually subsided

On June 9 treatment with imipramine was started again, the dose being increased to 75 mg t i d She again received occasional doses of quinalbarbitone 0 1 g as required The depression lessened, but after six weeks she began to complain of profuse sweating, and the dose was reduced to 50 mg t i d A week later, on July 25, she complained of a severe sore throat The throat was very red, without exudates or ulceration, and the cervical glands were tender on both sides Her temperature was 98°F, but had risen to 100°F next day The total white cell count was 1100 per c mm (neutrophils 4%, lymphocytes 92%, monocytes 4%) and the hæmoglobin was 14 4 g per 100 ml All drugs were stopped at once, and she was treated with penicillin and cortisone She made an uninterrupted recovery, and on the succeeding four days white-cell counts were 1200 (neutrophils 3%), 2100 (neutrophils 7%), 3100 (neutrophils 16%), and 9150 (neutrophils 63%) per c mm Over the next two weeks there was a neutrophil leucocytosis, with the total count rising to 27,000 per c mm , but since then the count has remained normal Her depression has now improved and she was recently discharged from hospital

The only drug this patient received, apart from imipramine, was quinalbarbitone, and the doses of this were small and infrequent Imipramine resembles in structure compounds of the phenothiazine group which are known to produce agranulocytosis and it would seem to have been the cause in this patient

Maudsley Hospital,
London, S E 5

SAMUEL I COHEN

CHEST X-RAYS AND RADIATION HAZARDS

SIR,—In 1957 the Ministry of Health issued a publication [1] on the development of the mass miniature radiography service and in 1959 a further memorandum [2] on radiological hazards to patients, which held that the value of mass radiography was so great that it should not be curtailed without good cause The radiation distributed by these X-ray machines was considered to make a negligible contribution to the total radiation to which the populace is exposed This statement is true, but although one can be reasonably sure there is little immediate hazard, the effect of small doses of radiation may have genetic consequences in the future In an atomic age the amount of unavoidable radiation that the populace receives will probably increase as time goes on Accidents similar to that at Windscale may happen again All radiation is dangerous, and it is the duty of those concerned to see that all unnecessary radiation is avoided What then of the future of the mass radiography using 35 mm camera units ?

The report on radiological hazards to patients quotes figures for the number of cases of tuberculosis found by this means in the whole of Great Britain in 1957 as a reason for continuing its use These figures were not further subdivided into areas, but it is obvious that the bulk of the cases came from the large cities

The same report also quotes the number of people X-rayed, and such figures have always been used to impress lay committees successfully These same committees should now be re-educated to realise that it is the results that matter and not the numbers X-rayed The successful unit is the one that can demonstrate how few people they have X-rayed to discover an appreciable number of new cases of tuberculosis It is unrealistic to try to justify the continued use of M M R units solely because of abnormalities other than tuberculosis Even as a measure to discover new cases of tuberculosis, it is relatively expensive and will become more so in the future In comparatively healthy areas 35 mm units could successfully be replaced by static and/or mobile 70 or 100 mm units mainly for the use of cases referred by general practitioners Crofton [3] felt that 35 mm camera units could still fulfil a useful purpose, but should be used less haphazardly Even in Edinburgh, however, the time will come when their use will have to be reconsidered

In some areas fluoroscopy sessions are used for the purpose of diagnosing chest disease This should be condemned o[illegible] right. The amount of radiation disseminated by each examination will vary considerably, but in any event will be substantially greater than the controlled dose given by radiography. Gibson[4] considered that routine fluoroscopy was no longer justified in the diagnosis of cardiac disease, owing to the high radiation dosage. It is even less justified as an initial means of diagnosing chest disease.

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[1] Morgan Hughes J A, He[illegible] Lancet 1960 i 552
[2] [illegible] Canad med Ass J 1960 82 1011

[1] H M (57) 9
[2] H M (59) 16
[3] Crofton J Brit med J Sept 3 1960 p 679

Finally, the use of chest X-rays in clinics could be reduced in certain cases. Children examined as contacts should not be X-rayed if their tuberculin test is negative. During pregnancy it is doubtful whether a routine chest X-ray is justified in the absence of symptoms; it could be delayed until the puerperium. The intervals for the routine surveillance of quiescent cases should also be reviewed at each attendance.

Quite obviously the extent by which irradiation can be reduced will vary in each area, but it is the concern of everyone to give the matter adequate thought at frequent intervals.

Bournemouth. O. D. BERESFORD.

WORKING WIVES—AND THEIR CHILDREN

SIR,—Your annotation last week showed great insight into the mental state of professional women tied to the household for some years.

Could we not find some way in our profession to enable women to retain their skill during the years when their children are small, by making part-time work more readily available?

I have in mind clinical assistantships in outpatient departments or a scheme whereby general practitioners accepted trainee assistants on a regular sessional basis.

Such part-time work, with sufficient remuneration to cover a reliable baby-minder, would go a long way to maintaining clinical interest during the critical 5 to 7 years before the youngest in the family is at school, when more work could be undertaken.

If the shortage of doctors, predicted by Professor Lafitte within the next decade, is to be avoided one obvious solution would surely be to make the fullest use of available part-time workers.

London, S.W.14. SYBILLE STOVIN.

SHORTAGE OF DIETITIANS

SIR,—I wonder if the recent King Edward's Hospital Fund memorandum on the shortage of dietitians, discussed in your annotation of Sept. 17, has received the notice it so urgently deserves. Those who read it will rightly regard it as a useful, though only preliminary, report and a balanced stimulus to more official action on this important subject which becomes increasingly related to many branches of modern therapy. The Professions Supplementary to Medicine Act may have a similar effect, though at first it seems to be mainly concerned with problems of registration, administration, and disciplinary procedures—with training facilities, &c., as mere afterthoughts.

Until recently the subject of dietetics seems to have escaped the attention of the Ministry of Health, and many doctors, both within and without the hospital service, have regarded this attitude as unrealistic.

Today the trained dietitian is quite often employed in the hospital service as a glorified cook with a not dissimilar rate of remuneration, and the reasons for this are probably (1) the present serious lack of trained dietitians, and (2) an incomplete knowledge of the subject by hospital staff.

The answer lies in the provision of adequate and well-considered training in dietetics throughout the country, and the present situation seems sufficiently serious to justify the setting up of a small body of inquiry to examine the present arrangements for the training of dietitians—which I suggest are appalling—and also the whole question of their employment, including remuneration and status. I suggest that the King Edward's Fund memorandum could form a most useful basis for any such inquiry.

London. J. SHARP GRANT.

*** A note about a Ministry memorandum on the duties of dietitians and the organisation of their work appears on p. 1202.—ED. L.

BROADER MEDICAL TEACHING

SIR,—I was much interested in Dr. Cardew's letter of Nov. 5 and subsequent correspondence because the subject is one which has always been very near to my heart and on which I have written a good deal.[1]

During the past twelve months, as a patient in a regional hospital and then a teaching hospital, I have been able to talk, at night, with many recently qualified men, and all of them expressed the same opinions as the general practitioners at the conference.

Surely the basic training during the clinical years is misdirected in aim, structure, and balance? Its general purpose should be to teach the student the general principles of medicine, to train him to a sufficient degree of skill to diagnose and treat common ailments in medicine and surgery, and to recognise conditions in which expert help is required, and so to orientate his attitude toward medicine that he can see the picture as a whole. He will quickly learn to look for aberrations from normal as they present themselves, and realise the importance of training his powers of observation on each case as it occurs. Then he will find out that taking a very careful history is the best way of coming to a sound conclusion.[2]

But today, in his clinical ward rounds and ward work generally, he is introduced to the patients of a *teaching hospital* where his mind is largely absorbed with the rarities of medicine. Now that several teaching hospitals have branches which are staffed like the central hospital but contain the everyday type of case, would it not be possible for the student's clinical and ward work to be undertaken at these branches, with visits to the main hospital weekly for instruction in the rarities? At present students get a completely false picture of the world outside—the world of the commonplace in which they are to spend their working lives.

Again, under present arrangements students are taught almost entirely by members of the hospital staff whose lives are spent almost entirely in their own specialty (which cannot conduce to a broad outlook). Is this really the best plan? Is there not much to be said for forming a school in the art of teaching, or for asking the universities to recommend men of outstanding ability in this field (with suitable remuneration) whose words would ring in the minds of students throughout their lives? In this connection the foundation of a department of general practice in teaching hospitals, as is done in the United States and Canada, has much to recommend it.

Dr. Cardew suggests that every teacher in the hospital service should spend a period in general practice first. I would go further and say that no doctor should be allowed to specialise without first doing a period outside hospital in general practice. The time to do this is immediately after qualification and registration: it would be very unsound to postpone the experience till later. The modern tendency in medicine, or nursing, is to think of patients

as case-numbers instead of *souls* (human entities) which is unfortunate if doctors of the future are to hold the same position of love and trust as did their forebears

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[4] Gibson, R. Cardiac Problems for Chest Physicians, p. 13. N.A.P.T. Symposium. London, 1958.

[1] Your Doctor of the Future. High Wycombe, 1953. State Medicine or What? London, 1952.

[2] Hunt, J. H. *Brit. Med. J.* 1957, i, 1076.

Worthing HAROLD LEESON

" ATHEROLIPID NUMBERS " AN EXPRESSION OF SERUM-CHOLESTEROL AND SERUM-LIPOPROTEIN RELATIONSHIPS

SIR,—Increases in serum-total-cholesterol and serum-beta-lipoproteins have been associated with clinical manifestations of atherosclerosis In addition, several investigators [1] [2] have observed absolute as well as relative decreases in alpha-lipoproteins in sera from atherosclerotic patients A consideration of these three lipid fractions may have clinical significance in this disease process Therefore, a mathematical relationship has been derived which is dependent upon concentrations of serum total, alpha-, and beta-lipoprotein cholesterol The value obtained from

$$\frac{\text{mg per 100 ml serum-total cholesterol} \times \dfrac{\text{mg per 100 ml beta lipoprotein cholesterol}}{\text{mg per 100 ml alpha lipoprotein cholesterol}}}{10}$$

has been termed the " atherolipid number "

Calculation of atherolipid numbers does not include a factor which ascribes greater significance to any one of the lipid fractions The divisor 10 has arbitrarily been used in this expression merely to limit the number of significant figures

To study the proposed relationship, serum-total-cholesterol as well as alpha- and beta-lipoprotein levels have been estimated eletrophoretically by the technique of Searcy et al [3] in over 1000 clinically healthy individuals This group included 554 males and 529 females ranging in age from 10 to 79 years Lipid values as well as ages were averaged for each decade Fig 1 demonstrates the effect of both sex and age upon serum-lipoprotein-cholesterol levels

In males there is a big rise in the serum total and beta-lipoprotein cholesterol in the third and fourth decades Females of corresponding age exhibit much smaller increases in these fractions It is noteworthy that in the post-menopausal decades, females averaged a higher serum-total and beta-lipoprotein cholesterol than males of the same age Oliver and Boyd [4] observed substantial increases in total cholesterol levels in 12 females aged 50–59 years as compared to both younger and older women In contrast, our studies employing a larger number of subjects failed to demonstrate a drop in serum-total-cholesterol levels in the post-menopausal decades A group of 69 women 60 years and over had an average serum total cholesterol of 302 mg per 100 ml compared to a mean of 304 mg per 100 ml in 74 females aged 50 to 59 years

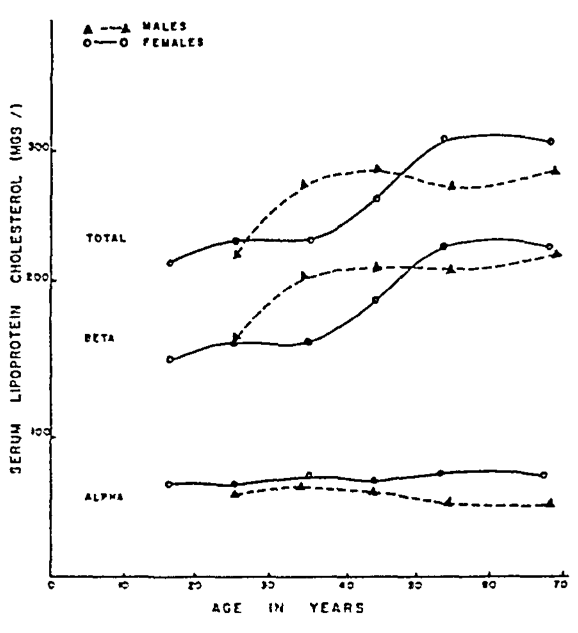

Fig 1—Serum-lipoprotein-cholesterol levels in clinically healthy individuals

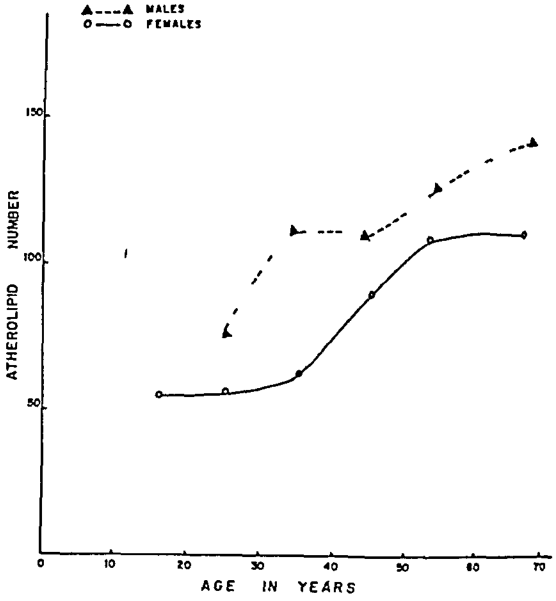

Fig 2—Atherolipid numbers in clinically healthy individuals

Lipid values obtained from the total study group have been used to calculate atherolipid numbers for subjects categorised according to sex and mean age Fig 2 shows that on the average atherolipid numbers of males are higher than those of females at all mean ages These data are in contrast to the lipoprotein cholesterol measurements, where females over the age of 50 had lipid values higher than males of corresponding age Reductions in alpha-lipoproteins in men of this age tend to increase the beta- to alpha-lipoprotein ratio thereby resulting in higher atherolipid numbers Such elevations in atherolipid numbers are consistent with the greater incidence of atherosclerotic complications in the male population and may suggest a possible relationship In females atherolipid numbers do not reach a maximum until after the menopause This peak again corresponds to the age at which women are more susceptible to myocardial infarction

Barr [5] has reported serum-total-cholesterol and distribution of this lipid fraction between alpha- and beta-lipoproteins in a group of myocardial infarction patients The average " atherolipid number " of 161 calculated from these data exceeds mean " atherolipid numbers " observed in our study group of clinically healthy individuals Therefore, a consideration of serum-total-cholesterol in addition to alpha- and beta lipoprotein measurements may aid in distinguishing atherosclerotic from normal subjects The significance of atherolipid numbers in a variety of disease states is now under investigation in our laboratories

R L SEARCY
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W H DAVIS
L M BERGQUIST

Los Angeles County Osteopathic Hospital
College of Osteopathic Physicians and
Surgeons Los Angeles and the
Cardiovascular Research Center Burbank
California

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1 Barr, D P Russ, E M, Eder H A *Amer J Med* 1951, **11**, 480
2 Oliver, M F, Boyd, G S *Brit Heart J* 1955 17 299
3 Searcy, R L Bergquist, L M, Jung R C, Craig, R, Korotzer, J *Clin Chem* (in the press)
4 Oliver M F Boyd G S *Brit Heart J* 1953 15, 3 7
5 Barr D P *Circulation* 1953 8 641

PROGNOSIS AND ANTICOAGULANT PROPHYLAXIS AFTER CORONARY OCCLUSION

SIR,—I should like to congratulate Professor McMichael and Dr Parry on their article of Nov 5—how well they have disposed of long-term anticoagulant therapy in patients with coronary occlusion

I believe that many physicians, like myself, are weak-minded, but few would care to admit it We are weak-minded because we yield to the requests of our patients and their relatives and prescribe anticoagulant drugs Relatives do not seem to mind if their loved ones die in my beds from a further coronary occlusion—and many of them do—provided they are having "blood-thinning drugs", but many questions have to be answered if these drugs have been withheld Similarly, if patients die from a further cardiac infarction any time after discharge from hospital, it is the doctors' fault for not continuing with these fashionable drugs The relatives say, "Smith next door is on these drugs and he is still alive, but my poor John has gone" Although without faith it is probable that some of us use these drugs occasionally for these reasons We may have been weak and wandering like lost sheep between New York, Edinburgh, and The London Hospital, but McMichael and Parry have given us strength and courage to remain static and adopt one course of action

For many years I have been teaching students that it is vitally important for patients with coronary occlusion to move their feet and legs at regular intervals and to do deep breathing exercises, and so to prevent phlebothrombosis and possible pulmonary infarction These measures are active substitutes for anticoagulants Some patients, however, are so fat, so stupid, or so stuporose that they will not do these exercises, and in these cases I believe anticoagulant therapy should be considered Others are so ill, so shocked and hypotensive that they cannot move their legs and in these patients anticoagulants are perhaps necessary

It is about time that we fully realised that anticoagulants cannot prevent *arterial* thrombosis No-one can persuade me that anticoagulants can postpone death from a further coronary occlusion I have witnessed too many deaths in patients whose prothrombin-times have been so perfect

McMichael and Parry have stabilised our views in their notable contribution and I only hope that a comparable article on short-term anticoagulant therapy will soon be forthcoming so that the disposal of these fashionable drugs may be completed

Cardiff BYRON EVANS

ODOUR OF POTASSIUM CYANIDE

SIR,—Professor Moncrieff's letter of Sept 3 refers to two papers in 1953 reporting that solutions of potassium cyanide were apparently odourless to 18% of white Australian males [1] and to 25% of males of the Luo and Kikuyu tribes in Kenya [2]

Some six years previously, Stock [3] stated that he too was insensitive to this odour, and indeed only 6 out of 11 workers in his laboratory could detect it Other authors [4] [5] suggested that 1 person in 2 or 4 in 5 could detect it, and Holmyard reported [6] that during 21 years at Clifton College, he examined some hundreds of boys and that approximately 3 out of 5 found an odour I then tested 20 adult white males and 20 females with a newly opened bottle of potassium cyanide crystals For each sex, 16 subjects reported an odour, but few non-technical persons recognised it [7]

It therefore seems evident that a substantial proportion of a population is unable to detect this odour, characteristic though it is Howe [8] found it wise to have a suitable assistant beside him in his laboratory to advise him of any escape of cyanogen gas Professor Gatterman is reported [4] as having advised—in 1904—the smoking of a cigar to facilitate the detection of cyanogen Sachs,[9] who is insensitive to the smell of cyanide in the normal way, smokes a cigarette and records a "very nasty taste" in the presence of cyanide or cyanogen gas

There are now of course reliable instruments which can be used to monitor cyanogen or hydrogen cyanide gases, but their use is not always practicable—or even necessary in cases such as the above

Winthrop Laboratories,
Newcastle upon Tyne J R GWILT

HEATSTROKE

SIR,—I was very interested in your editorial of Oct 15, but would most certainly agree with Wing-Commander Mortimer (Nov 5) that it is perfectly possible to treat severe hyperpyrexia successfully without elaborate equipment, and it would be very unfortunate if doctors suddenly faced with such a desperate emergency were to be inactive or delay treatment because of a feeling of futility with the resources they had

In these circumstances the best method to reduce temperature does seem to be the encouragement of evaporation of artificial sweat at all costs

While doing my National Service I was for a short time involved in the medical care of British Forces in the Jordan port of Akaba on the Red Sea A relatively unacclimatised airman suddenly collapsed semi-conscious and delirious on the beach with heatstroke He was immediately sponged all over with what must have been warm water from available water-bottles, and his colleagues and my R A M C orderlies fanned him vigorously with their towels to create a reasonably good air current He was then moved by stretcher vehicle about a mile to a small Army Hospital where we had facilities by courtesy of the Jordan Arab Army During the journey the sponging was continued and, of course, the air current supplied by the movement of the vehicle Once in hospital it was possible to continue treatment more vigorously with a small electric fan and recovery, though slow, was thereafter uneventful

Edinburgh A G M CAMPBELL

PERITONEAL DIALYSIS IN SALICYLATE INTOXICATION

SIR,—Dr Elliott and Dr Crichton (Oct 15) described the use of peritoneal dialysis in human salicylate intoxication, much as Ettledorf et al [10] used it in the dog The differences in the solutions account for the difference in the amount dialysed Ettledorf et al, using albumin as a dialysing fluid, succeeded in their best experiment in removing 19% of the salicylate dose Dr Elliott and Dr Crichton point out "in retrospect we had hoped to wash out salicylates by dialysis but we believe we accomplished more by providing available base as a vehicle for enhancement of renal excretion of conjugated glycuronide"

We felt there is no need for an extra dialyser if the patient's own dialyser (the kidney) could be exploited to its maximum

In experiments on rabbits and dogs we used tris (hydroxymethyl) amino-methane (T H A M) (Abbott) by infusion to promote salicylate excretion This buffer alkalinises urine and increases urine output It has been used in the treatment of respiratory acidosis [11] In a 7 kg dog given 1875 mg of salicylate intravenously (blood-level 59 mg per 100 ml), an excretion of 1232 mg of salicylate in the urine was induced by an intra-

as case-numbers instead of *souls* (human entities) which is unfortunate if doctors of the future are to hold the same position of love and trust as did their forebears

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[1] Kirk R L Stenhouse N S *Nature Lond* 1953 171 698
[2] Allison A C *Man* 1953, 53 23
[3] Stock J A *Chem & Ind* 1947, p 262
[4] Francis F G *ibid* p 325
[5] Unstead Joss L G L *ibid* p 294
[6] Holmyard E J *ibid* p 294
[7] Gwilt, J R *ibid* p 325
[8] Howe, J L *ibid* p 374
[9] Sachs W *ibid* p 358
[10] Etteldorf J N Montalvo J M Kaplan S Sheffield J A *J Pediat* 1960, 56 1
[11] Brinkman G L Remp D G Coates E O, McCall Priest, E *Amer J med Sci* 1960, 239 341

Worthing HAROLD LEESON

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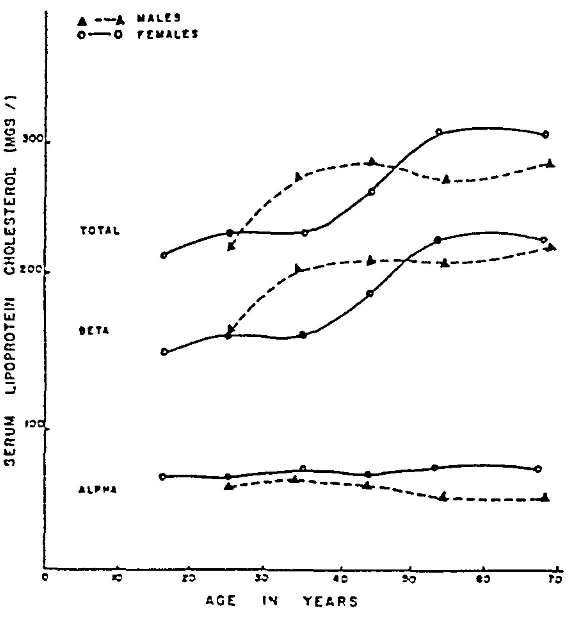

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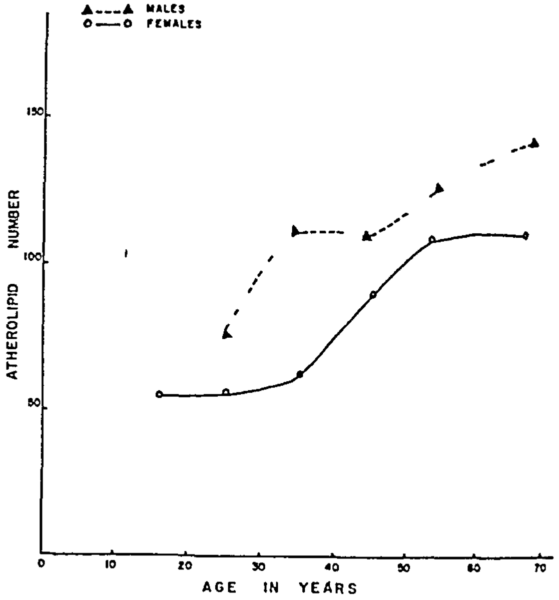

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[1] Barr, D P, Russ, E M Eder H A *Amer J Med* 1951, 11, 480
[2] Oliver, M F, Boyd, G S *Brit Heart J* 1955 17, 299
[3] Searcy, R L, Bergquist, L M, Jung, R C, Craig, R, Korotzer, J *Clin Chem* (in the press)
[4] Oliver M F Boyd G S *Brit Heart J* 1953 15 387
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I believe that many physicians, like myself, are weak-minded, but few would care to admit it We are weak-minded because we yield to the requests of our patients and their relatives and prescribe anticoagulant drugs Relatives do not seem to mind if their loved ones die in my beds from a further coronary occlusion—and many of them do—provided they are having "blood-thinning drugs", but many questions have to be answered if these drugs have been withheld Similarly, if patients die from a further cardiac infarction any time after discharge from hospital, it is the doctors' fault for not continuing with these fashionable drugs The relatives say, "Smith next door is on these drugs and he is still alive, but my poor John has gone" Although without faith it is probable that some of us use these drugs occasionally for these reasons We may have been weak and wandering like lost sheep between New York, Edinburgh, and The London Hospital, but McMichael and Parry have given us strength and courage to remain static and adopt one course of action

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Cardiff BYRON EVANS

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Some six years previously, Stock [3] stated that he too was insensitive to this odour, and indeed only 6 out of 11 workers in his laboratory could detect it Other authors [4] [5] suggested that 1 person in 2 or 4 in 5 could detect it, and Holmyard reported [6] that during 21 years at Clifton College, he examined some hundreds of boys and that approximately 3 out of 5 found an odour I then tested 20 adult white males and 20 females with a newly opened bottle of potassium cyanide crystals For each sex, 16 subjects reported an odour, but few non-technical persons recognised it.[7]

It therefore seems evident that a substantial proportion of a population is unable to detect this odour, characteristic though it is Howe [8] found it wise to have a suitable assistant beside him in his laboratory to advise him of any escape of cyanogen gas Professor Gatterman is reported [4] as having advised—in 1904—the smoking of a cigar to facilitate the detection of cyanogen Sachs,[9] who is insensitive to the smell of cyanide in the normal way, smokes a cigarette and records a "very nasty taste" in the presence of cyanide or cyanogen gas

There are now of course reliable instruments which can be used to monitor cyanogen or hydrogen cyanide gases, but their use is not always practicable—or even necessary in cases such as the above.

Winthrop Laboratories,
Newcastle upon Tyne J R GWILT

HEATSTROKE

SIR,—I was very interested in your editorial of Oct 15 but would most certainly agree with Wing-Commander Mortimer (Nov 5) that it is perfectly possible to treat severe hyperpyrexia successfully without elaborate equipment, and it would be very unfortunate if doctors suddenly faced with such a desperate emergency were to be inactive or delay treatment because of a feeling of futility with the resources they had

In these circumstances the best method to reduce temperature does seem to be the encouragement of evaporation of artificial sweat at all costs

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Edinburgh. A G M CAMPBELL

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SIR,—Dr Elliott and Dr Crichton (Oct 15) described the use of peritoneal dialysis in human salicylate intoxication, much as Etteldorf et al [10] used it in the dog The differences in the solutions account for the difference in the amount dialysed Etteldorf et al, using albumin as a dialysing fluid, succeeded in their best experiment in removing 19% of the salicylate dose Dr Elliott and Dr Crichton point out "in retrospect we had hoped to wash out salicylates by dialysis but we believe we accomplished more by providing available base as a vehicle for enhancement of renal excretion of conjugated glycuronide"

We felt there is no need for an extra dialyser if the patient's own dialyser (the kidney) could be exploited to its maximum

In experiments on rabbits and dogs we used tris (hydroxymethyl) amino-methane (T.H.A.M.) (Abbott) by infusion to promote salicylate excretion This buffer alkalinises urine and increases urine output It has been used in the treatment of respiratory acidosis [11] In a 7 kg dog given 1875 mg of salicylate intravenously (blood-level 59 mg per 100 ml), an excretion of 1232 mg of salicylate in the urine was induced by an intra-

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5 Unstead Joss L G L. *ibid* p 294
6 Holmyard E. J *ibid* p 294
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8 Howe J L. *ibid* p 374
9 Sachs W *ibid* p 358
10 Etteldorf J N., Montalvo, J M. Kaplan, S Sheffield, J A *J Pediat* 1960 56 1
11 Brinkman G L., Remp D G Coates E.O., McCall Price, E. *Amer J med Sci* 1960 239 341

as case-numbers instead of *souls* (human entities) which is unfortunate if doctors of the future are to hold the same position of love and trust as did their forebears

Worthing. HAROLD LEESON

"ATHEROLIPID NUMBERS" AN EXPRESSION OF SERUM-CHOLESTEROL AND SERUM-LIPOPROTEIN RELATIONSHIPS

SIR,—Increases in serum-total-cholesterol and serum-beta-lipoproteins have been associated with clinical manifestations of atherosclerosis In addition, several investigators[1] [2] have observed absolute as well as relative decreases in alpha-lipoproteins in sera from atherosclerotic patients A consideration of these three lipid fractions may have clinical significance in this disease process Therefore, a mathematical relationship has been derived which is dependent upon concentrations of serum total, alpha-, and beta-lipoprotein cholesterol The value obtained from

$$\frac{\text{mg per 100 ml serum-total-cholesterol} \times \dfrac{\text{mg per 100 ml beta lipoprotein cholesterol}}{\text{mg per 100 ml alpha lipoprotein cholesterol}}}{10}$$

has been termed the "atherolipid number"

Calculation of atherolipid numbers does not include a factor which ascribes greater significance to any one of the lipid fractions The divisor 10 has arbitrarily been used in this expression merely to limit the number of significant figures

To study the proposed relationship, serum-total-cholesterol as well as alpha- and beta-lipoprotein levels have been estimated electrophoretically by the technique of Searcy et al[3] in over 1000 clinically healthy individuals This group included 554 males and 529 females ranging in age from 10 to 79 years Lipid values as well as ages were averaged for each decade Fig 1 demonstrates the effect of both sex and age upon serum-lipoprotein-cholesterol levels

In males there is a big rise in the serum total and beta-lipoprotein cholesterol in the third and fourth decades Females of corresponding age exhibit much smaller increases in these fractions It is noteworthy that in the post-menopausal decades, females averaged a higher serum-total and beta lipoprotein cholesterol than males of the same age Oliver and Boyd[4] observed substantial increases in total cholesterol levels in 12 females aged 50–59 years as compared to both younger and older women In contrast, our studies employing a larger number of subjects failed to demonstrate a drop in serum total-cholesterol levels in the post-menopausal decades A group of 69 women 60 years and over had an average serum-total-cholesterol of 302 mg per 100 ml compared to a mean of 304 mg per 100 ml in 74 females aged 50 to 59 years

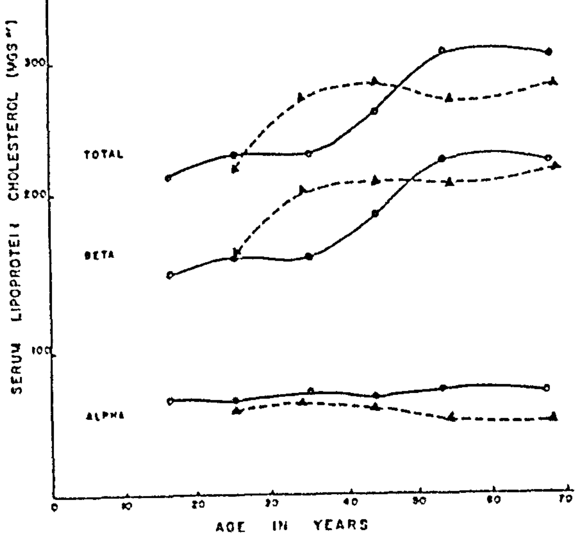

Fig 1—Serum lipoprotein-cholesterol levels in clinically healthy individuals

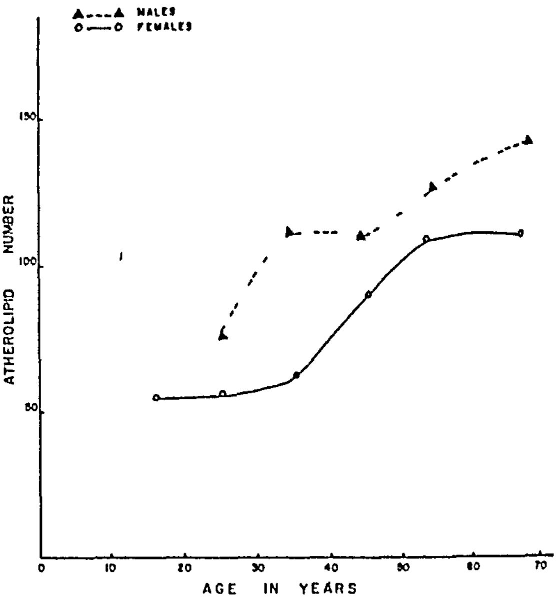

Fig 2—Atherolipid numbers in clinically healthy individuals

Lipid values obtained from the total study group have been used to calculate atherolipid numbers for subjects categorised according to sex and mean age Fig 2 shows that on the average atherolipid numbers of males are higher than those of females at all mean ages These data are in contrast to the lipoprotein cholesterol measurements, where females over the age of 50 had lipid values higher than males of corresponding age Reductions in alpha-lipoproteins in men of this age tend to increase the beta- to alpha-lipoprotein ratio thereby resulting in higher atherolipid numbers Such elevations in atherolipid numbers are consistent with the greater incidence of atherosclerotic complications in the male population and may suggest a possible relationship In females atherolipid numbers do not reach a maximum until after the menopause This peak again corresponds to the age at which women are more susceptible to myocardial infarction

Barr[5] has reported serum-total-cholesterol and distribution of this lipid fraction between alpha- and beta lipoproteins in a group of myocardial infarction patients The average "atherolipid number" of 161 calculated from these data exceeds mean "atherolipid numbers" observed in our study group of clinically healthy individuals Therefore, a consideration of serum-total-cholesterol in addition to alpha- and beta lipoprotein measurements may aid in distinguishing atherosclerotic from normal subjects The significance of atherolipid numbers in a variety of disease states is now under investigation in our laboratories

R L SEARCY
V P CARROLL II
W H DAVIS
L M BERGQUIST

Los Angeles County Osteopathic Hospital College of Osteopathic Physicians and Surgeons Los Angeles and the Cardiovascular Research Center, Burbank California

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11. Brinkman, G. L., Remp, D. G., Coates, E. O., McCall Priest, E. *Amer. J. med. Sci.* 1960, 239, 341.

venous infusion of THAM, and the serum-salicylate fell to 29 mg per 100 ml in four hours. The same animal, given another 1875 mg of salicylate intravenously, put out 198 mg of salicylate in the urine in four hours on a lactate-saline intravenous infusion, reducing the plasma salicylate from 55 to 41 mg per 100 ml. This material is apparently non-toxic to humans and we intend to carry out clinical trials in salicylate intoxication.

Clinical Investigation Unit,
Children's Hospital of Winnipeg

SYDNEY ISRAELS
HAROLD DAVIES

LECTURES IN HÆMATOLOGY

SIR,—Your review (Nov. 5) of *Lectures on Hæmatology* states that the potential reader could "buy a whole textbook of hæmatology, containing nearly everything in this volume and a lot more, for rather less." In justice to the contributing lecturers I feel compelled, as editor of the volume in question, to point out that this statement is specifically untrue. The bulk of the material appearing in the lectures is not yet available in any current general hæmatological text with which I am familiar, certainly not in the texts of Whitby and Britton, Wintrobe, de Gruchy, Sturgis, Bernard and Bessis, Storti, Heilmeyer and Begemann, or Leavell and Thorup, and most of these works are, in any case, substantially more expensive.

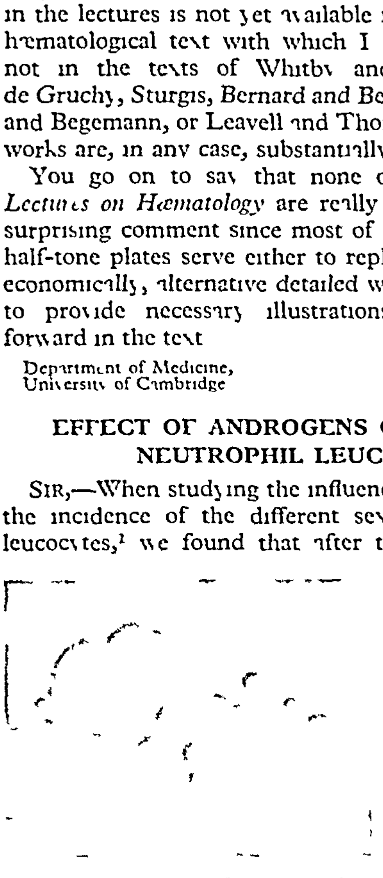
You go on to say that none of the illustrations in *Lectures on Hæmatology* are really necessary. This is a surprising comment since most of the line diagrams and half-tone plates serve either to replace, more clearly and economically, alternative detailed written descriptions, or to provide necessary illustrations of arguments put forward in the text.

Department of Medicine,
University of Cambridge

F. G. J. HAYHOE

EFFECT OF ANDROGENS ON NUCLEI OF NEUTROPHIL LEUCOCYTES

SIR,—When studying the influence of sex hormones on the incidence of the different sex-chromatin forms in leucocytes,[1] we found that after ten days of androgen treatment, the frequency of C forms, which usually number about 2–3% in infantile male rats, reached 12%, a value characteristic of the mature male. The incidence of forms A (drumstick) and B was not affected by the administration of androgens.[3] This finding and the changes of the sex-chromatin pattern seen after castration[2] led us to the conclusion that the incidence of the so-called pseudoforms was closely related to maturation—i.e., to an androgen effect.



After repeating and extending our experiments, we have now established that after a long period of androgen treatment the nuclear configuration of certain leucocytes also shows a characteristic change, in addition to the increased number of the pseudoforms C (small clubs, rackets).

The most conspicuous alteration is a focal condensation of the nuclear substance showing increased basophilia, which is clearly visible in smears stained with a Giemsa solution (see figure). There are usually several round or ovoid condensations in the nuclear substance, giving an indented appearance to the nuclear surface, resembling a blackberry or a bunch of grapes. These "blackberry" forms were later found not only in male animals but also in female rats treated with androgen and also in three female patients receiving intensive androgen treatment for mammary carcinoma.

Since these "blackberry" forms could not be observed after treating rats of either sex with œstrogen, progesterone, or cholesterol, we believe that they may be regarded as a morphological sign of an increased androgen level.

Department of Pathology,
Medical University,
Pécs, Hungary

CH. MÉHES
ST. ZSIFKOVITS
C. JOBST

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[1] Jobst, C., Zsifkovits, S., Méhes, C. [illegible] (in the press).
[2] Pf[illegible], G. Zbl. Gynäk. 1960, 82, 220.
[3] Zsifkovits, S., Méhes, C., Jobst, C. [illegible] Lond. 1959, 184, 1239.

NEPHROPATHY DURING PHENINDIONE THERAPY

SIR,—Toxic effects due to phenindione used for short-term or long-term anticoagulant therapy are rare. The commonest forms are fever, rash, and agranulocytosis. Jaundice has also been reported,[1] [2] and so has prolonged and severe diarrhœa with steatorrhœa.[3] A case of agranulocytosis complicated by proteinuria and uræmia was described by Kirkeby.[4] Most reports of renal damage have been in the nature of hints, such as the case of Kirkeby, but two further cases have been recorded.[5] [6]

The first of these was a case of dermatitis, hepatitis, and nephritis during phenindione therapy. The renal features were albuminuria and granular casts with red and white cells in the urine.

Barritt and Jordan[6] describe a fatality during treatment of pulmonary embolism with phenindione. Renal tubular necrosis was assumed to be due to the anticoagulant drug. Fever and diarrhœa were present, with oliguria, anuria, and raised blood-urea. Necropsy showed extensive tubular necrosis.

The following example of diarrhœa and nephrotic syndrome arose during "long-term anticoagulant therapy" with phenindione.

In 1959 a professional man of 59, previously of good health, had a myocardial infarct, for which he was treated with phenindione. Treatment was continued after the first month in doses sufficient to keep the prothrombin at a "therapeutic level." The dose averaged 50 mg. to 75 mg. per day. The patient had 6 weeks' holiday after convalescence. During the last 3 weeks he had severe diarrhœa, which did not respond to any remedy. He continued to take his phenindione.

After 2 weeks of diarrhœa his legs began to swell, and became progressively worse. The hands were involved to a less extent. At this stage he was admitted to hospital. Massive œdema of legs and thighs was present, with ascites and bilateral pleural effusions at the bases. No rise in venous pressure was present. The heart was clinically normal, blood pressure 140/80 mm. Hg. There were no retinal changes. The urine was loaded with albumin and contained hyaline casts. The serum-electrolytes were normal, the blood-urea was 52 mg. per 100 ml. and serum-cholesterol 200 mg. per 100 ml. The peripheral blood-picture was normal. The stools contained no pathogens or occult blood, and their fat content was normal.

The diarrhœa was regarded as due to phenindione, and the drug was immediately stopped. The diarrhœa lessened, and ceased after 4 days. None of the known causes was found for the "nephrotic syndrome", and it was strongly suspected that this was also due to phenindione.

Treatment with prednisone 30 mg. a day resulted in a gradual diuresis and general improvement. The pleural effusions and ascites absorbed, and the legs were free of œdema in 4 weeks. The serum-albumin level improved, but the albuminuria persisted in varying but considerable quantities.

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[1] Last, F. N., Beattie, [illegible] Canad. med. Ass. J. 195[illegible], 7[illegible], 10[illegible].
[2] B[illegible], C., Desmond, F. B. N.Z. med. J. 195[illegible], 57, [illegible].
[3] Juel-Jensen, B. E. Brit. med. J. 1959, ii, 173.
[4] Kirkeby, K. Lancet, 19[illegible], i, 580.
[5] B[illegible], R. H., Call[illegible], H. B. Ann. intern. Med. 19[illegible], 52, [illegible].
[6] Barritt, D. W., Jordan, S. C. Lancet, 19[illegible], i, [illegible].

The patient has continued in good general health on continuous prednisone therapy in smaller dosage This was gradually reduced to as little as 5 mg a day for 5 days a week, but this resulted in swelling of the feet once more Between 5 and 10 mg daily seems to be sufficient for control, but has had no appreciable effect on the albuminuria The patient is now fully employed, and feels well in every way

The 3 weeks' uncontrollable diarrhœa ceased within a few days of stopping phenindione It is reasonably clear that this feature was due to the drug, and was similar to that described by Juel-Jensen It seems reasonable also to blame the drug for the nephropathy Renal damage has been described previously during administration of phenindione Observation of the patient for 10 months has revealed none of the usual causes of the nephrotic syndrome For this to arise from some other cause during the period of a recognised toxic feature (diarrhœa) seems unlikely coincidence The evidence for renal damage disappeared after stopping the drug in Brooks and Calleja's patient Recovery might have occurred in this case had the drug been stopped at the first sign of toxicity It seems that persisting with the drug during the period of diarrhœa led to permanent renal damage

Other anticoagulants have been used less extensively perhaps, but so far do not seem to have been responsible for such grave toxic effects It seems desirable to use one of the alternative preparations, or to keep a close eye on the urine for albumin during phenindione therapy

Dewsbury General Hospital,
Yorkshire

GODFREY B TAIT

TYPE-14 ECHO VIRUS AND INFANTILE GASTROENTERITIS

SIR,—In July, 1959, three babies in a nursery had gastroenteritis with bloody stools From rectal swabs 13 strains of Echo virus type 14 were isolated in the three children and in twenty contacts This virus has occasionally been isolated in sporadic infantile diarrhœa,[1] but here it was epidemic Such an epidemic, but due to Echo virus type 18, was recorded in premature babies in 1958[2]

On July 19, two infants, 9 and 14 months old, suddenly developed symptoms of gastroenteritis with fever, dehydration, and bloody stools The same syndrome appeared 48 hours later in a third child of 16 months All three recovered after rehydration in 5 to 8 days Stool cultures showed no pathogenic bacteria no shigella, no salmonella, or any of the serological types of *Escherichia coli* usually isolated in infantile gastroenteritis Inoculation of rectal swabs on primary cultures of monkey-kidney cells from *Cynocephalus babuin* induced the cytopathogenic effect of enteroviruses The three strains did not grow, at first passage, on primary human amniotic cells They showed no effect on KB cells They were not pathogenic for suckling mice

They were neutralised by an antiserum prepared in rabbits with the Tow reference strain of Echo virus type 14 There was no neutralisation with Echo antisera 1–13 kindly supplied by the National Foundation for Infantile Paralysis

By rectal swabs 10 other strains of Echo virus type 14 were isolated from twenty children living in the same nursery Among the non-carriers two showed serological evidence of infection The carriers had no symptoms or signs except for a stationary weight for three or four weeks

The sera of the three patients were challenged by seroneutralisation against 100 TCD_{50} of Echo virus type 14 Two of them had a significant rise in antibody between acute and convalescent sera, from none to a titre of 1/40 The third patient developed no antibodies, the virus was present in the fæces for at least three weeks, after which the child could no longer be followed

Seven of the ten healthy carriers, studied at different times, had neutralising antibodies in their sera

This survey shows that Echo virus type 14 can be highly contagious in a nursery Infection by this virus may be manifested in infants by gastroenteritis

Institut Pasteur, Paris

P LEPINE

J SAMAILLE
J MAURIN
O DUBOIS
M C CARRE

Institut Pasteur, Lille

GONADAL DYSGENESIS (TURNER'S SYNDROME) WITH MALE PHENOTYPE AND XO CHROMOSOMAL CONSTITUTION

SIR,—It is a pity that Dr Bloise and his colleagues (Nov 12) described their patient under the primary heading of Turner's syndrome This was originally described in females and embodies various characteristic clinical features When the XO chromosomal constitution was demonstrated in 1959 by Ford and his colleagues, they emphasised again that the patients were female but had an abnormal genotype

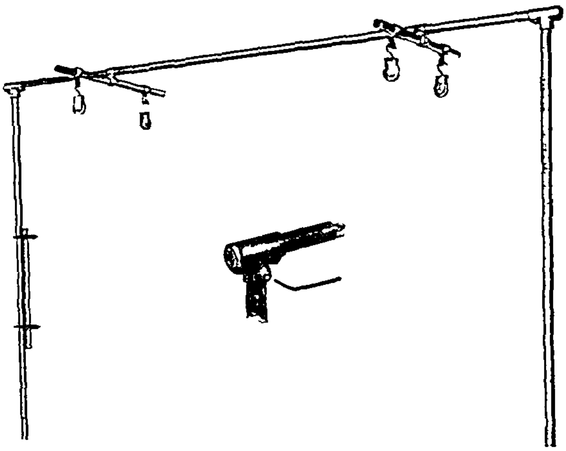
Dr Bloise's patient has a male phenotype and apparently none of the clinical features of Turner's syndrome The diagnosis seems to rest entirely on the XO chromosomal constitution If, as this case suggests, there may be other syndromes associated with an XO constitution, would it not prevent future confusion to reserve the diagnosis of Turner's syndrome for females who show the clinical features of it?

Cambridge

LAURENCE MARTIN

CHILD'S OVERHEAD FRAME

SIR,—The accompanying illustration shows an overhead frame for the treatment of fractures of the shaft of the femur, and of burns of the buttock, by the gallows method in children below the age of five This frame can be adapted to suit any size of child's cot There are no protruding nuts and bolts to be undone by other children in the ward, and the frame can be erected in a matter of minutes by the nurse The screws are countersunk, are not amenable to damage, and cannot be undone without the use of the special key provided



This frame has been made for me by the London Splint Co , 69, Weymouth Street, London, W 1

Guy's Hospital
London S E 1

G A MARIN

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[1] Ramos Alvarez M Sabin A B *J Amer med Ass* 1958 167 147
[2] Eichenwald H F Abadio A , Arky, A M Hartman A P *J Amer med Ass* 1958 166, 1563

POSTPARTUM PRE-ECLAMPSIA

SIR,—I have read Mr Theobald's letter in your issue of Nov 19 The homœostatic changes characteristic of toxæmia affect the solvent (water) and the electrolyte (sodium) The evidence I have already adduced incriminates a predominant mechanism in their production—a diversion of the renal circulation causing ischæmia of the cortex An action of the tubules brought about by hormonal influences cannot be held primarily responsible for these changes [1]

The obstetrician must not be beguiled into believing that toxæmia is anything but a single entity by the fact that pregnancy can occur in association with acute or chronic glomerular nephritis, nephrosis, essential hypertension, phæochromocytoma, beriberi, cerebral hæmorrhage, or any other incidental and recognisable disease

Worthing JOHN SOPHIAN

A MASSIVE OVARIAN CYST

SIR,—In a competitive spirit, I should like to report an enormous ovarian cyst It may be surpassed in weight alone, but I shall be surprised if it can be beaten as regards the ratio of weight to body-weight

A Fijian woman, aged 32, was admitted to this surgical unit in July, 1959 Since the birth of twins 2 years before she had noticed a symptomless lower abdominal swelling, which had enlarged at a uniform rate until 3 months before admission to hospital It had then grown more quickly, becoming associated with malaise and discomfort from the increased weight and size (see figure) The patient's weight was 250 lb

An ovarian cyst was the obvious diagnosis, but the appearance was not much different from the massive leiomyoma reported by Clinton-Thomas [2] An intravenous pyelogram was therefore arranged, but, as the renal outlines could not be demonstrated on the preliminary plain film, the examination was abandoned (Dr H F Knowles)

At operation through an incision running from the xiphisternum to the symphysis pubis, a way into the peritoneal cavity was found just below the xiphisternum, and the abdomen was opened through its length There were adhesions—some quite thick—between the cyst and the parietes When these were divided carefully, the massive cyst was traced down to the left fallopian tube, the pedicle being about 2 in wide After removal of the cyst a superabundance of abdominal wall remained After dissection well back off the recti, a large amount of skin was excised, and the recti were then overlapped completely throughout their length This tightened up the abdominal wall fairly well

Postoperative progress was uneventful, the patient's general condition improved, and her weight after operation was 103 lb —indicating that the cyst weighed about 147 lb As an outpatient a month later her weight was 109 lb

The histopathological report (Dr M I Gosden) read "Fibrous tissue wall lined with a single layer of cuboidal epithelium There is no evidence of malignant change"

When seen in May, 1960, the patient's weight was 130 lb, and she felt particularly well The abdominal wall had tightened up appreciably although there was still some slack skin

This case shows the harmful effect of pressure alone, as indicated by the calculated weight-loss The precise explanation is uncertain, although presumably pressure on vital organs—thoracic and abdominal—played an important part

I wish to thank Dr P W Dill Russell, C B E, director of medical services for Fiji, for permission to publish this case report

Lautoka Hospital,
Lautoka, Fiji J M FORTMAN

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[1] Sophian J Lancet Nov 12 1960 p 1086
[2] Clinton-Thomas C L Brit J Surg 1956, 43, 197

LOCAN PESSARIES IN THE TREATMENT OF TRICHOMONAL VAGINITIS

SIR,—Certain points in the interesting paper by Dr Eckersley and his colleagues (Sept 3) deserve comment For example, that anything less than two 'Locan' pessaries in 24 hours would not be expected to be effective [1] When this was given, their results with locan were identical with those obtained with the control, acetarsol It is inferred that acetarsol is much less toxic than locan, but how far is this from the truth? In the past few years many reports of serious toxic effects of acetarsol pessaries have appeared, these include frequent vomiting, purpura and other rashes, encephalopathy, and unconsciousness, in addition to one fatal poisoning [2-5] One cannot avoid the conclusion that acetarsol is such a toxic substance compared with any of those in locan that its use should be avoided when another equally or more effective preparation is available which does not cause such dangerous complications In spite of this, they recommend that locan should not be used on the grounds of sensitisation and reaction

This view was supported by Dr Scott-Gray (Sept 17), who quoted her colleague, Dr Marjorie Murrell [6] With reasonable results from any drug, we cannot hope to get away from personal preferences in its use The evidence for the side-effects referred to by your contributors was not supported by our own observations In Murrell's short series, 3 cases of eczema of the vulva were encountered, but there was no evidence that this was due to sensitisation to any of the ingredients of locan, local anæsthetic or other In a case of our own, there was at first discomfort but treatment was persisted in and as the lesion improved, this initial effect disappeared In Dr Eckersley's series, there seems to have been 1 true case of allergic sensitisation, in the remaining 4, treatment was stopped immediately Only the first of the 5 cases had a rash, suggesting true allergy, but the application of local anæsthetics to other mucous membranes, such as the eye, can cause initial discomfort until the surface is anæsthetised

Like ours, theirs was a satisfactory trial, and the fact that the time and frequency of relapses were the same for each preparation, shows that the population treated was similar in each instance

The paper by Dr Eckersley and his colleagues supports recent symposia and the paper by Catterall and Nichol [7] which have emphasised the need to treat both partners if relapse is to be avoided It may well be that the results from treatment with locan and acetarsol are the maximum that can be obtained until this can be achieved

Owing to improved formulation the activity in locan against trichomonas and other pathogens has recently been increased by a factor of 10 without any increase in the amounts of the active ingredient, which should reduce the time of exposure necessary to the allegedly sensitising chemicals, or enable a reduction in their amount

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[1] Stewart H C, Hughes, W H Thomas J G, Nixon V C W *Lancet* 1957, ii, 1038
[2] White, A *Brit med J* 1956 ii 1528
[3] Pearson A *ibid* 1958, i 310
[4] *ibid* July 16 1960, p 217
[5] Acheson J *ibid* Aug 20 1960 p 603
[6] Murrell, M *Lancet* 1957, ii 1285
[7] Catterall R D, Nichol C S, *Brit med J* 1960 i 1177

Although we cannot agree with the conclusions drawn, we are glad that they have been contradicted by the data quoted in the body of the paper which so well support the efficiency of locan treatment

Departments of
Pharmacology and Bacteriology,
St. Mary's Hospital Medical School,
London W.2

H C STEWART
W HOWARD HUGHES

TREATMENT OF TENSION PNEUMOTHORAX

SIR,—The immediate treatment of tension pneumothorax seems still to be widely misunderstood by those who see this condition in its early stages The necessity for continuous pleural decompression is appreciated but the method commonly used to achieve this is inefficient and dangerous An emergency not infrequently seen by the thoracic surgeon is the patient, bloated with surgical emphysema and gasping for breath, with that anachronism "the indwelling needle" dangling uselessly from his chest. Any needle from lumbar puncture to French's transfusion seems to be used All, even including Foster-Carter's which was designed for the purpose, are inefficient, uncomfortable, and dangerous

The objections to the use of a needle are threefold

(1) Whatever its size, by its very nature, a needle cannot be big enough to cope with the large volumes of air coming from a major leak. The insertion of a needle brings immediate, but temporary, relief Air however, cannot escape fast enough, pressures again rise, and air is forced into the tissues along the needle track. Soon the whole apparatus is floated out of the pleura into the chest wall as the skin lifts on a rising tide of surgical emphysema. Decompression ceases and the tension pneumothorax is re-established

(2) Whether the point is sharp or blunt the rigid needle may puncture the lung as it expands—particularly the fragile tissue of bullous emphysema

(3) A needle cannot be fixed satisfactorily into the chest. Adhesive tape, corks, perforated bottle caps, or plastic shields are some of the favourite methods None is secure or comfortable

The only safe way to decompress the pleural space is through a rubber catheter about size 10 Jaques inserted, usually, in the second intercostal space anteriorly The technique is simple provided that the position for the catheter is checked by the preliminary aspiration of air The tube is inserted through a stab wound with the aid of a trocar and cannula A generous length is passed into the space, the catheter is attached to the skin and is then connected to an underwater seal Such a tube will carry off large volumes of air, cannot slip out, will not damage the lung, and by its flexibility permits the patient to be moved in comfort A similar tube can be used in an infant suffering from a staphylococcal tension pyopneumothorax.

I do not apologise for labouring a point that may be familiar to many There are still too many patients whose lives are jeopardised and whose treatment is unnecessarily prolonged by the use of these inefficient methods

Tension pneumothorax is usually a simple mechanical problem which will respond to the application of simple mechanical principles The apparatus necessary for the insertion of an intercostal catheter should be part of the standard equipment on every medical ward

Regional Thoracic Unit
Brook Hospital
London S.E.18

A M MACARTHUR.

Obituary

JAMES BURNETT RAE

M B Aberd

Dr Burnett Rae, who died on Oct. 31 at the age of 80, was for many years vice-chairman of the Churches Council of Healing, which, with the late Archbishop Temple, he helped to found A few days before he died he was elected vice-president of the Council

He was born in Edinburgh, but his father, the late John Rae, J P, was an Aberdonian, and he was educated in Aberdeen He graduated M B in 1902, but after postgraduate studies in theology at New College, Edinburgh, he spent several years as assistant minister at Sefton Park Presbyterian Church Liverpool Against this background, his service with the R A M C during the 1914–18 war not unnaturally led him to share in the pioneer work on the treatment of functional and nervous disorders He became consulting psychotherapist to Queen Alexandra's Hospital, Millbank, and medical officer in charge of the psychotherapy department at the Cambridge Hospital, Aldershot

After the war he continued to work in this new specialty, and he was a member of the staff of the Croydon General Hospital and the Institute for the Scientific Treatment of Delinquency He also lectured for the National Association for Mental Health But his interest in pastoral therapy was the centre of his practice, and of this side of his life E E C writes

"Burnett Rae was a superb example of a man who practised what he preached Not that he preached often, though he was always willing to occupy a pulpit on such occasions as Hospital Sunday St Luke's day or a series of addresses on health and faith He believed that Medicine and the Church have complementary tasks, and he strove to help Medicine to realise that its work was incomplete if the spiritual factor was omitted in treatment He was always open to believe that God would and did intervene in the course of illness So much he used to say, occurs which we cannot explain, let us therefore rejoice when a patient learns the vital secret of faith and his illness clears up He himself once had a spot on the lung which he firmly believed resolved through prayer and his own faith He believed that when he was examining his patients he was in fact 'laying on hands'—such was his approach He was a wonderful raconteur and always had a fund of apt illustrations He was also a good listener, and many found that just to talk to him did them good A dear loving friend and truly a 'beloved physician'"

Appointments

BOLAND MARY K. M.B N.U.I D.C.H. assistant M O.H St. Helens, Lancashire.

CONSTABLE, F L M.D B.SC.Durh consultant bacteriologist Royal Victoria Infirmary Newcastle upon Tyne.

HUGHES, J T M.B.Manc. M R C.P D C.P assistant neuropathologist (S.H.M O) Radcliffe Infirmary Oxford.

ORR J M B M.B assistant M O.H and school M O, Ipswich

PEARSON VERONICA M.B Cantab D OBST D C.H assistant M O Halifax.

WOODMANSEY A. C. M.D Leeds, M.R.C.P D.P.M D C.H consultant in child psychiatry Sheffield Regional Hospital Board and United Sheffield Hospitals

Leeds Regional Hospital Board

DAVID J D P M.D B.SC. Wales consultant in geriatrics Pontefract and Wakefield area hospitals

ELLETT BROWN HAROLD B.M Oxon D.P M consultant psychiatrist and deputy physician superintendent De la Pole Hospital Willerby

HAMILTON MARGARET G M.B Belf S.H.M O in pathology Harrogate area hospitals

LAMONT S M.B F.F.A R.C.S D.A consultant in anaesthetics Leeds area hospitals

NEWCOMBE, JOHN M.B Lond. D.P M consultant in psychiatry and medical superintendent York group of mental-deficiency hospitals

Colonial Appointments

BLACKMAN VICTOR M.B Lond D.P.H., D C.P specialist (clinical pathologist) Uganda

DOS SANTOS, W A M.B Camb., DIP.BACT government bacteriologist and pathologist Barbados

GEMMELL, W R M.B Glasg D.M.S Bechuanaland

SANSOM, J F., M.B Lond M O B S I.P

STEVENSON MAUDE, M.D Belf., D C.H. M.O Bahamas

Notes and News

SUPPLEMENTARY ESTIMATES

THE supplementary estimate for the National Health Service in the current financial year[1] shows an increase for England, Wales, and Scotland of £42,900,000, bringing the total net cost to £626,400,000 Of this, £41 million is needed to meet the increased remuneration for doctors recommended by the Royal Commission £24 million is to cover arrears, and the balance of £17 million represents the cost of a year's increments

DIETITIANS

THE Ministry of Health, in conjunction with King Edward's Hospital Fund for London, has lately surveyed the work of dietitians Suggestions for the more effective use of their specialised knowledge are contained in a memorandum[3] from the Ministry

The dietitian should be relieved of unskilled work in order that she may act more as an adviser and instructor Her duties should include drawing up diet sheets, calculating individual inpatient diets, compiling therapeutic diets with the catering officer, providing recipes for special dishes, training diet cooks, interviewing and instructing patients in wards and discussing patients' dietaries with ward sisters, advising catering officers on the nutritive value and suitability of menus, advising outpatients, assisting in teaching nurses and others, and performing any dietary surveys requested by the medical staff Light, vegetarian, religiously determined, and some gastric diets do not need direct supervision by the dietitian, though she can assist in their planning Menu planning by dietitians for the main catering in hospitals not only ensures that the dietary is appropriate but results in less work, as requests for special diets are fewer and use can be made of food from the main kitchen for therapeutic diets

The present shortage of dietitians may make it necessary to employ one dietitian for a group of hospitals The Ministry regards this, not as a temporary expedient, but as a logical development

ORTHOPÆDICS AT OXFORD

Professor Trueta last December set himself what must have proved a satisfying task—that of reviewing orthopædics at Oxford up to the end of his first ten years as Nuffield professor[4]

The first holder of this chair was G R Girdlestone, one of the band of men who became disciples of Sir Robert Jones before, during, and just after the first world war It was Girdlestone who founded a regional orthopædic service at Oxford on the basis of a central hospital (the original " Wingfield ") with peripheral clinics in the neighbouring towns, and this scheme has been a model for orthopædic services elsewhere in the country Through his friendship with Lord Nuffield, he established what came to be known as the Wingfield-Morris Orthopædic Hospital with all its ancillary services devoted to the treatment, rehabilitation, and education of long-stay orthopædic patients

Girdlestone was succeeded as Nuffield professor in 1940 by H J Seddon, who brought increased renown to Oxford orthopædics in his work, particularly on peripheral nerve injuries and poliomyelitis In the few years after the war before he became director at the Royal National Orthopædic Hospital, surgeons from abroad had already become eager to work with him at the Wingfield-Morris

In 1949 he was followed by Professor Trueta, under whose guidance the importance of research, not only in itself but as an integral part of the training of every orthopædic surgeon, has been given new impetus With further help from Lord Nuffield, a great new building has appeared which houses the outpatient department, records office, radiological department, and lecture hall as well as the research laboratories and offices of the university department proper Yet another baptism was called for, and the old Wingfield-Morris with the new buildings and extensions has become the Nuffield Orthopædic Centre

Among Professor Trueta's interesting ideas for the future is that the Nuffield centre should be placed officially " at the disposal of the orthopædic specialists of the whole region, from consultants to junior staff " The consultants at the periphery should have opportunities at the centre, including charge of beds where they can study their cases of special interest with all the research facilities at their disposal and without the hurry and anxiety of overloaded clinics and emergency interruptions The difficulty of obtaining junior staff in regional hospitals can, Professor Trueta thinks, be mitigated by a system of exchange for part of their time of service between those working in the periphery and the trainees at the centre itself Only by increasing the attractiveness of such appointments in this way can we hope to stimulate the best men to enter on the long climb to surgical consultancy and reverse our increasing dependence on foreign aid to fill the junior posts in non-teaching hospitals

MANCHESTER MEDICAL GAZETTE

THE *Manchester University Medical School Gazette* has marked the 62nd year of its existence by a change of title, its new name reflects its increasing circulation among graduates In the first issue of the *Manchester Medical Gazette*,[1] devoted mainly to education, Dr J R Ellis writes on " preparation for medicine as a profession " (an abridged version of his Wood Jones lecture, extracts from which we published in our issue of Nov 12), Dr R F L Logan on " general practice tomorrow ", and Mr A R Anscombe on " clinical teaching ", and a thoughtful critique of the preclinical course is contributed by a medical student

If the high standard of the first number is maintained, the *Gazette* will undoubtedly fulfil its aim of interesting Manchester students and graduates, and all the medical men practising in Manchester

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University of Cambridge

On Nov 12 the degree of M B was conferred on R H C Vaux

University of Leeds

On May 18 the honorary degree of D SC will be conferred on Prof C H G Macafee

University of Aberdeen

Dr Mary Scott has been appointed to a lectureship in physiology

University of Wales

At recent examinations for the D T C D the following were successful

Aftab Ahmed, J O W Ang Awa, Ghalam Azam Chowdhury, Panchkari Ghosh Dastidar, Chelliah Kulanayagam, Mankavil Kovilveetil Karunakara Menon, Jyothinagaram Thimmaraya Chetty Ramalingam

Royal College of Surgeons of England

On Dec 7, at 2 30 P M , at the college, Lincoln's Inn Fields, W C 2, Sir Stanford Cade will give a Bradshaw lecture He will speak on Malignant Melanoma On Dec 8, at 5 P M , Mr H J Seddon will give a Robert Jones lecture His subject will be the Manchester Ship Canal and the Colonial Frontier

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the Faculty on Nov 7, the following officers were elected

President, Dr J H Wright, visitor, Prof C F W Illingworth, hon Secretary, Dr Gavin B Shaw, hon Treasurer, Mr R B Wright, hon Librarian, Dr A L Goodall, representative on the General Medical Council, Prof D F Cappell, representative on the General Dental Council, Prof W Malcolm Gibson, councillors, Dr G J Aitken, Dr W Ferguson Anderson, Prof Roland Barnes, Mr Thomas Gibson, Dr A D Telford Govern Prof T Symington, Dr T J Thomson

Mohamed Abdel Kader Mansour was admitted as a fellow of Faculty *qua* surgeon The Macewen medal was awarded to Dr I W Young

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[1] 1960 61 Supplementary Estimate Civil Estimates H M Stationery Office 1960 Pp 9 95

[2] See *Lancet* Sept 17 1960 p 636

[3] *H M* (60) 91

[4] Lecture delivered by Prof J Trueta at the Nuffield Orthopædic Centre Oxford on Dec 3, 1959

[1] *Manchester Medical Gazette* vol 40 no 1 October 1960 Edited by E S Rosen B Sc Obtainable from the Medical School, The University, Manchester 13 Annual subscription 10s 6d

University of London

The following have passed the final examination for the M.B , B S

Honours —G M Besser (*b d*), St. Bartholomew's D J Galton (*b*), University College Margaret L Jones (*d*), St. Mary's H A Lee (*c,d*), King's College P H Millard (*d*), University College Jennifer P Peebles (*e*), Guy's Hospital B A Senewiratne (*b*) University College

(*b*) distinguished in medicine (*c*) distinguished in applied pharmacology and therapeutics (*d*) distinguished in surgery, (*e*) distinguished in obstetrics and gynæcology

Pass —R O Addae, Adeoye Ademiyi, F P Adler, Ardan Andan M F Anderson W C Annoff, E N Armitage, P M Ashby, Susan M Atherton A F J Atkins, B N Ballantine, R B Barrett, J L Beecher, Audrey J Bickham, W H C Berry, Margaret L Birtwistle, R G Black Shirley M Blackman, P D Blade A R H Bliss Sonia G Bolton Shirley A Bond David Booth J G Bradbrooke, C L Bray William Brown M D Burgess Evelyn M J Callis, B J Camp H M Carpenter, I P Cast, B Wan Bun Chan John Chapman K G A Clark Jane M Clegg N M Cole, Heather J Collins, Pauline T Combe, Derek Corless Dorothy K Cory, J C Craggs Jennifer Craig Michael Cullotty, J C Cummins D J W Darby, Margaret Davidson, Gareth Davies Gillian M Davies, P B M Davis R S Dawkins, A D Dean J M Dinham P G J Dobson I S Duff Diana Dutton J D Eddy D P Edmunds, D A Edwards R W England, A W G English, P R Evans, C B Everett Ann D Fairclough, H M Fisher D J Fishlock, R A Forster, J V Fowles Joanna M Fraser Stanley Freedman, Gillian Freeman Sebastian Freudenberg Jill Fyfield Gillian A Garnett J A Garrod A R Geach Penelope A Gething, Sheila M Girvan W A Gould, Patricia A Green Patricia E L Greenlaw J L Grogono Pamela M Haigh, Joyce C Hall-Tomkin, Josephine E Hammond R G Harding N F Harley R I Harrison J C Hasler, J D Hatton I B Hayter J B Hicks, G T Hollingworth D A Hollis Alison M Holloway P T Horder A S Horniblow E R Howard D P M Howells David Hughes, C N Hughes Jane E Hughes, J P Hughes M S Hughes D M Hunter, Joanna E Hunter J A Hunter Pamela J Hunter, A C M Inwald, R M Jeffery K A Johansen, M L Jones, P A Jones, Winifred A Kane J H Kiff A W Kilroy David King D P E Kingsley, Kwamena Kyei-Mensah, T R Lawson D A Lee, Sheila J Lees Thomas Lehner, Eveline B McCulley, R H Mackeith, R F M McKenzie, A C MacLean D R Macnair W J McNeilly, K M A Madgwick, M P Madigan E J B Makin, Baru Malek, Elaine M Maliphant, Eli Babajiva Mama Deirdre H Marlow G S Martinez, Bridgett A Mason R J Meco,, Joanna Merry, G M Michael Felicity A Milburn, M H Millward R D G Milner, C A L Moon John Moore, R W Morris Ursula V L Morris, J D Morrison C W Mortimer P B Mudge, F G M Musleh J F O A I Mustaffah, T G Nash, H G Naylor M I M Noble, J R Norman, Margaret A Nunan Ezekwe Ojinmah C N Payne, Ann Parker J B R Parker Rosemary C Partington, Sheila M Pask, J P Patten, J F Pearson John Pearson Heather Pell H G Peters A H Pickering D A Pocock, C J F Pool, A E Pratt R B Prescott, Edward Proctor Vajra Promatvethi Yvonne F Ransley, Jacqueline J Rees, J H K Reeves D S Restall, R S Richardson Anne P Roberts J R Robson I C Roddick P J Sanderson, Thomas Sherwood, Ann Simpson I P Slee, D H Smith, Patrick Smith P H Sönksen C J Spivey D J Stern A F S Stewart, H J S Sugden, D R Sutherland D J M Taylor G W Thomas, W H Thomas R G N Thomson, Sheila M Thwaites Angela R Till Isobel Tomkins, F D Trevarthen Wendell Tsao P L H Vernon Harvey Wagman, C J S Walter, G G Ward, R J Warner P H Waterfield, A V Watkins C L W Webb Diana V A Whitaker M M Wicks Wendy E Williams D G Willits D P Winter, Margaret Woodford, Rosemary J Wool F M Young Ting Chiu Yu.

Royal College of Surgeons in Ireland

On Nov 17 the fellowship of the college was conferred on H. B Devlin, D G Kelly, and W J Twibill

College of General Practitioners

At the annual general meeting of the college on Nov 19, Dr Annis Gillie, chairman of council, said that more than 6000 members and associates had joined since its foundation—nearly 700 during the past year There were now 35 faculties, 25 in the United Kingdom and Eire, 4 in New Zealand, 1 in Kenya, and 5 in South Africa where a South African Council of the college was soon to be formed The special committee, under Sir Harry Jephcott, had raised £345,000 in a few months

Dr G F Abercrombie was re-elected president. Sir Harry Jephcott was appointed an honorary fellow Dr G L Hindson (Northumberland) was presented with the Butterworth gold medal for 1959–60

General agreement was obtained to the proposed memorandum and articles of association of the new incorporated college

At a meeting of the new council, held later, Dr Annis Gillie was re-appointed chairman, Dr K M Foster, vice-chairman, Dr H L Glyn Hughes, hon treasurer, and Dr J H Hunt hon secretary

Dinner to Dr W N Pickles

After the war the doctors of Wensleydale met several times at the home of Dr Pickles in Aysgarth to discuss the proposed health service Out of those meetings grew the annual doctors' party, usually held in late spring to which each year Dr Pickles invited a guest speaker On Oct 22 Dr and Mrs Pickles were themselves the guests of all those whom they had entertained at their spring parties During the dinner, which was held at Leyburn, presentations were made to them both

Clinical Aspects of Genetics

The Royal College of Physicians of London have chosen this subject as the theme of their next conference, which will be held on March 17 and 18 It is primarily arranged for fellows and members who are consultants in medicine or pathology

The speakers will include Dr J A Fraser Roberts, Dr J N Walton, Dr Eliot Slater, Dr C O Carter, Dr C E Ford, Prof P E Polani, Dr W M Court Brown, Prof L S Penrose, Dr Marco Fraccaro, Prof C E Dent, Prof Harry Harris, Dr Charles Burnett, Dr H Lehmann, Dr R B McConnell, Dr R T C Pratt, and Dr C A Clarke Numbers may have to be limited, and application should be made to the Registrar at the College, Pall Mall East, S W 1, not later than Jan 23 The entrance fee is five guineas, which should not be sent with the application

Congress of the International Diabetes Federation

This congress will be held in Geneva from July 10 to 14 Particulars may be had from the secretary general of the congress Dr Bernard Rilliet, 4, boulevard des Tranchees, Geneva, Switzerland

International Federation of Gynæcology and Obstetrics

A world congress of this Federation will be held from Sept 3 to 9 in Vienna Further particulars may be had from the scientific secretary of the Federation, Dr V Grünberger, Alserstrasse 4, Vienna IX, Austria.

Quaker Medical Society

On Wednesday, Nov 30, at 8 30 P M , at Friends House, Euston Road, London, N W 1 Dr Cuthbert Dukes will give a Lister lecture His subject will be Dr John Fothergill (1712–1780) and his Medical Contemporaries

Proctologica Latina Collegium

An international meeting of colon and anorectal surgery is to be held by this body from May 18 to 20 in Tangier Further particulars may be had from the general secretary of the collegium, Dr G B E Simonetti, 3, via S Raffaele, Milan, Italy

International Congress for Microbiology

This congress will be held at Montreal, from Aug 19 to 25, 1962 There will be five sections—structure and function, agricultural microbiology, industrial microbiology, medical and veterinary microbiology, and virology Inquiries should be sent to Dr N E Gibbons, National Research Council, Ottawa 2, Canada

Richard Kovacs Prize

The first award of this prize has been made by the Royal Society of Medicine to Dr Philippe Bauwens Dr Bauwens will receive the prize and deliver a lecture on May 10

The prize, which has been established by Mrs Ina Kovacs in memory of her husband, the late Dr Richard Kovacs, is to be awarded triennially for work in physical medicine

British Diabetic Association

On Oct 14–15 the medical and scientific section of this Association met in Glasgow The first day was devoted to a colloquium on prediabetes, including 14 papers One suggestion made was a trial of the sulphonylureas in human prediabetes, and the committee of the section is now planning such a trial On the second day there was a paper and discussion on the care of elderly diabetics, followed by 7 further papers The meeting was well attended, and Dr Jorgen Pedersen, of Copenhagen, was a guest speaker

Anglo-French Exchange Bursaries

Applications are invited for bursaries to be awarded in 1961 to young British doctors under the exchange scheme arranged by the French Embassy in London between the Institut National d'Hygiene in Paris and the Ciba Foundation in London

The grants (870 francs a month) will be awarded for two to four months to medical men who wish to obtain clinical experience or carry out research in France. Application forms may be had from the director of the Ciba Foundation 41 Portland Place London, W 1 The closing date for applications is Jan 31

Notes and News

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The dietitian should be relieved of unskilled work in order that she may act more as an adviser and instructor Her duties should include drawing up diet sheets, calculating individual inpatient diets, compiling therapeutic diets with the catering officer, providing recipes for special dishes, training diet cooks, interviewing and instructing patients in wards and discussing patients' dietaries with ward sisters, advising catering officers on the nutritive value and suitability of menus, advising outpatients, assisting in teaching nurses and others, and performing any dietary surveys requested by the medical staff Light, vegetarian, religiously determined, and some gastric diets do not need direct supervision by the dietitian, though she can assist in their planning Menu planning by dietitians for the main catering in hospitals not only ensures that the dietary is appropriate but results in less work, as requests for special diets are fewer and use can be made of food from the main kitchen for therapeutic diets

The present shortage of dietitians may make it necessary to employ one dietitian for a group of hospitals The Ministry regards this, not as a temporary expedient, but as a logical development

ORTHOPÆDICS AT OXFORD

Professor Trueta last December set himself what must have proved a satisfying task—that of reviewing orthopædics at Oxford up to the end of his first ten years as Nuffield professor [4]

The first holder of this chair was G R Girdlestone, one of the band of men who became disciples of Sir Robert Jones before, during, and just after the first world war It was Girdlestone who founded a regional orthopædic service at Oxford on the basis of a central hospital (the original " Wingfield ") with peripheral clinics in the neighbouring towns, and this scheme has been a model for orthopædic services elsewhere in the country Through his friendship with Lord Nuffield, he established what came to be known as the Wingfield-Morris Orthopædic Hospital with all its ancillary services devoted to the treatment, rehabilitation, and education of long-stay orthopædic patients

Girdlestone was succeeded as Nuffield professor in 1940 by H J Seddon, who brought increased renown to Oxford orthopædics in his work, particularly on peripheral nerve injuries and poliomyelitis In the few years after the war before he became director at the Royal National Orthopædic Hospital, surgeons from abroad had already become eager to work with him at the Wingfield-Morris

In 1949 he was followed by Professor Trueta, under whose guidance the importance of research, not only in itself but as an integral part of the training of every orthopædic surgeon, has been given new impetus With further help from Lord Nuffield, a great new building has appeared which houses the outpatient department, records office, radiological department, and lecture hall as well as the research laboratories and offices of the university department proper Yet another baptism was called for, and the old Wingfield-Morris with the new buildings and extensions has become the Nuffield Orthopædic Centre

Among Professor Trueta's interesting ideas for the future is that the Nuffield centre should be placed officially " at the disposal of the orthopædic specialists of the whole region, from consultants to junior staff " The consultants at the periphery should have opportunities at the centre, including charge of beds where they can study their cases of special interest with all the research facilities at their disposal and without the hurry and anxiety of overloaded clinics and emergency interruptions The difficulty of obtaining junior staff in regional hospitals can, Professor Trueta thinks, be mitigated by a system of exchange for part of their time of service between those working in the periphery and the trainees at the centre itself Only by increasing the attractiveness of such appointments in this way can we hope to stimulate the best men to enter on the long climb to surgical consultancy and reverse our increasing dependence on foreign aid to fill the junior posts in non-teaching hospitals

MANCHESTER MEDICAL GAZETTE

THE *Manchester University Medical School Gazette* has marked the 62nd year of its existence by a change of title, its new name reflects its increasing circulation among graduates In the first issue of the *Manchester Medical Gazette*,[1] devoted mainly to education, Dr J R Ellis writes on " preparation for medicine as a profession " (an abridged version of his Wood Jones lecture, extracts from which we published in our issue of Nov 12), Dr R F L Logan on " general practice tomorrow ", and Mr A R Anscombe on " clinical teaching ", and a thoughtful critique of the preclinical course is contributed by a medical student

If the high standard of the first number is maintained, the *Gazette* will undoubtedly fulfil its aim of interesting Manchester students and graduates, and all the medical men practising in Manchester

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University of Cambridge

On Nov 12 the degree of M B was conferred on R H C Vaux

University of Leeds

On May 18 the honorary degree of D SC will be conferred on Prof C H G Macafee

University of Aberdeen

Dr Mary Scott has been appointed to a lectureship in physiology

University of Wales

At recent examinations for the D T C D the following were successful

Aftab Ahmed, J O W Ang Awa, Ghalam Azam Chowdhury, Panchkari Ghosh Dastidar, Chelliah Kulanayagam, Mankavil Kovilveetil Karunakara Menon, Jyothinagaram Thimmaraya Chetty Ramalingam

Royal College of Surgeons of England

On Dec 7, at 2 30 P M, at the college, Lincoln's Inn Fields, W C 2, Sir Stanford Cade will give a Bradshaw lecture He will speak on Malignant Melanoma On Dec 8, at 5 P M, Mr H J Seddon will give a Robert Jones lecture His subject will be the Manchester Ship Canal and the Colonial Frontier

Royal Faculty of Physicians and Surgeons of Glasgow

At a meeting of the Faculty on Nov 7, the following officers were elected

President, Dr J H Wright, visitor, Prof C F W Illingworth, hon Secretary, Dr Gavin B Shaw, hon Treasurer, Mr R B Wright, hon Librarian, Dr A L Goodall, representative on the General Medical Council, Prof D F Cappell, representative on the General Dental Council, Prof W Malcolm Gibson, councillors, Dr G J Aitken, Dr W Ferguson Anderson, Prof Roland Barnes, Mr Thomas Gibson, Dr A D Telford Govan, Prof T Symington, Dr T J Thomson

Mohamed Abdel Kader Mansour was admitted as a fellow of Faculty *qua* surgeon The Macewen medal was awarded to Dr I W Young

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[1] 1960 61 Supplementary Estimate Civil Estimates H M Stationery Office 1960 Pp 9 9d

[2] See *Lancet* Sep 17, 1960 p 636

[3] H M (60) 91

[4] Lecture delivered by Prof J Trueta at the Nuffield Orthopædic Centre Oxford on Dec 3 1959

[1] *Manchester Medical Gazette* vol 40 no 1, October 1960 Edited by E S Rosen B Sc Obtainable from the Medical School, The University, Manchester 13 Annual subscription 10s 6d

University of London

The following have passed the final examination for the M.B , B.S

Honours—G M Besser (b d) St Bartholomew's D J Galton (b) University College Margaret L Jones (d), St Mary's H A Lee (c,d) King's College P H Millard (d) University College Jennifer P Peebles (e), Guy's Hospital B A Senewiratne (b) University College.

(b) distinguished in medicine (c) distinguished in applied pharmacology and therapeutics, (d) distinguished in surgery (e) distinguished in obstetrics and gynæcology

Pass—R O Addie, Adeoye Adeniyi F P Adler Andrew Anderson M F Anderson W C Anoff E N Armitage, P M Ashby, Susan M Atherton A F J Atkins, B N Ballantine, R B Barrett J L Beecher Audrey J Beckham, W F C Berry Margaret L Birtwistle, R G Black, Sheila M Blackman, P D Blade A R H Bliss Sonia G Bolton Shirley A Bond, David Booth J G Bradbrooke, C L Bray, William Brown M D Burgess, Evelyn M J Callis, B J Camp H M Carpenter I P Cast B Wan-Bun Chan John Chapman K G A Clark, Jane M Clegg N M Cole, Heather J Collins, Pauline T Combe, Derek Corless Dorothy K Cox, J C Craggs, Jennifer Craig Michael Cullow, J C Cummins D J W Dare, Margaret Davidson Gareth Davies Gillian M Davies, P B M Davis R S Dawkins, A D Dean J M Dinham P G J Dobson I S Duff Diana Duron J D Eddy D P Edmunds D A Edwards, R W England A W G English P R Evans C B Everett, Ann D Fairclough H M Fisher, D J Fishlock, R A Forster, J N Fowles, Joanna M Fraser Stanley Freedman Gillian Freeman Sebastian Freudenberg Jill Fyfield Gillian A Garnett, J A Garrod A R Geeson Penelope A Gething Sheila M Girvan W A Gould Patricia A Green Patricia E L Greenlaw J L Grogono, Pamela M Haigh Joyce C Hall-Tomkin Josephine E Hammond R G Hardner N F Harley, R I Harrison J C Hasler J D Hatch I B Haver J B Hicks, G T Hollingworth D A Hollis Alison M Holloway P T Horder A S Hornblow E R Howard, D P M Howells David Hughes, G N Hughes, Jane E Hughes, J P Hughes M S Hughes, D M Hunter, Joanna E Hunter, J A Hunter Pamela J Hunter, A C M Inwald R M Jeffery K A Johansen M L Jones, P A Jones, Winifred A Kane, J H Kiff A W Kilroy David King D P E Kingsley, Kwamena Kyei-Mensah T R Lawson, D A Lee, Sheila J Lees Thomas Lehner Eveline B McCulley R H McKeith R F M McKenzie, A C MacLean D R Mann W J McNeilly K M A Madgwick, M P Madigan E J B Makin, Bryan Malek, Elaine M Maliphant Eli Babajiva Mann Deirdre H Marlow G S Martinez, Bridgett A Mason R J Mecoy Joanne Merry, G M Michael Felicity A Milburn M H Millward R D G Milner, C A L Moon John Moore, R W Moran Ursula V L Morris, J D Morrison C W Mortimer P B Mudge, F G M Muslen J F O A I Mustafah T G Nash, H G Naylor, M I M Noble, J R Norman, Margaret A Nunan, Ezekwe Ojinmah C N Paine, Ann Parker J B R Parker Rosemary C Parrington, Sheila M Pask, J P Patten J F Pearson, John Pearson, Heather Pell H G Peters A H Pickering D A Pocock, C J F Pool, A E Pratt R B Prescott Edward Proctor Vajn Promavethi Yvonne F Ranley Jacqueline J Rees, J H K Reeves D S Restall R S Richardson, Anne P Roberts J R Robson I C Roddie, P J Sanderson, Thomas Sherwood, Ann Simpson I P Slee, D H Smith, Patrick Smith P H Sonksen C J Spivey D J Stern A F S Stewart, H J S Sudgen D R Sutherland D J M Taylor G W Thomas, W H Thorne R G N Thomson Sheila M Thwaites, Angela R Till Isobel Tomkins, F D Trevarthen Wendell Tsao P L H Vernon Harvey Wagman, C J S Walter, G G Ward R J Warner P H Waterfield, A V Watkins, C L W Webb Diana N A Whitaker M M Wicks Wendy E Williams D G Willis D P Winter Margaret Woodford, Rosemary J Wool, F M Young Ting Chiu Yu.

Royal College of Surgeons in Ireland

On Nov 17 the fellowship of the college was conferred on H. B Devlin, D G Kelly, and W J Twibill

College of General Practitioners

At the annual general meeting of the college on Nov 19, Dr Annis Gillie, chairman of council, said that more than 6000 members and associates had joined since its foundation—nearly 700 during the past year There were now 35 faculties, 25 in the United Kingdom and Eire, 4 in New Zealand, 1 in Kenya, and 5 in South Africa where a South African Council of the college was soon to be formed The special committee, under Sir Harry Jephcott had raised £345,000 in a few months

Dr G F Abercrombie was re-elected president. Sir Harry Jephcott was appointed an honorary fellow Dr G L Hindson (Northumberland) was presented with the Butterworth gold medal for 1959–60

General agreement was obtained to the proposed memorandum and articles of association of the new incorporated college

At a meeting of the new council held later, Dr Annis Gillie was re-appointed chairman, Dr K. M Foster, vice-chairman, Dr H L Glyn Hughes, hon treasurer, and Dr J H Hunt hon secretary

Dinner to Dr W N Pickles

After the war the doctors of Wensleydale met several times at the home of Dr Pickles in Aysgarth to discuss the proposed health service Out of those meetings grew the annual doctors' party usually held in late spring to which each year Dr Pickles invited a guest speaker On Oct 22 Dr and Mrs Pickles were themselves the guests of all those whom they had entertained at their spring parties During the dinner, which was held at Leyburn presentations were made to them both

Clinical Aspects of Genetics

The Royal College of Physicians of London have chosen this subject as the theme of their next conference which will be held on March 17 and 18 It is primarily arranged for fellows and members who are consultants in medicine or pathology

The speakers will include Dr J A Fraser Roberts, Dr J N Walton, Dr Eliot Slater, Dr C O Carter, Dr C E Ford, Prof. P E Polani, Dr W M Court Brown, Prof L S Penrose, Dr Marco Fraccaro, Prof C E Dent, Prof Harry Harris, Dr Charles Burnett, Dr H Lehmann, Dr R. B McConnell, Dr R. T C Pratt, and Dr C A Clarke. Numbers may have to be limited, and application should be made to the Registrar at the College, Pall Mall East, S W 1, not later than Jan 23 The entrance fee is five guineas, which should *not* be sent with the application

Congress of the International Diabetes Federation

This congress will be held in Geneva from July 10 to 14 Particulars may be had from the secretary general of the congress Dr Bernard Rilliet, 4, boulevard des Tranchees, Geneva, Switzerland.

International Federation of Gynæcology and Obstetrics

A world congress of this Federation will be held from Sept 3 to 9 in Vienna Further particulars may be had from the scientific secretary of the Federation, Dr V Grünberger, Alserstrasse 4 Vienna IX Austria

Quaker Medical Society

On Wednesday, Nov 30, at 8.30 P M , at Friends House, Euston Road, London, N W 1, Dr Cuthbert Dukes will give a Lister lecture His subject will be Dr John Fothergill (1712–1780) and his Medical Contemporaries

Proctologica Latina Collegium

An international meeting of colon and anorectal surgery is to be held by this body from May 18 to 20 in Tangier Further particulars may be had from the general secretary of the collegium, Dr G B E Simonetti, 3, via S Raffaele, Milan Italy

International Congress for Microbiology

This congress will be held at Montreal, from Aug 19 to 25, 1962 There will be five sections—structure and function, agricultural microbiology, industrial microbiology, medical and veterinary microbiology, and virology Inquiries should be sent to Dr N E Gibbons, National Research Council, Ottawa 2, Canada

Richard Kovacs Prize

The first award of this prize has been made by the Royal Society of Medicine to Dr Philippe Bauwens Dr Bauwens will receive the prize and deliver a lecture on May 10

The prize, which has been established by Mrs Ina Kovacs in memory of her husband, the late Dr Richard Kovacs, is to be awarded triennially for work in physical medicine.

British Diabetic Association

On Oct. 14–15 the medical and scientific section of this Association met in Glasgow The first day was devoted to a colloquium on prediabetes, including 14 papers One suggestion made was a trial of the sulphonylureas in human prediabetes, and the committee of the section is now planning such a trial On the second day there was a paper and discussion on the care of elderly diabetics, followed by 7 further papers The meeting was well attended, and Dr Jorgen Pedersen, of Copenhagen, was a guest speaker

Anglo-French Exchange Bursaries

Applications are invited for bursaries to be awarded in 1961 to young British doctors under the exchange scheme arranged by the French Embassy in London between the Institut National d'Hygiene in Paris and the Ciba Foundation in London

The grants (870 francs a month) will be awarded for two to four months to medical men who wish to obtain clinical experience or carry out research in France. Application forms may be had from the director of the Ciba Foundation, 41 Portland Place London W 1 The closing date for applications is Jan. 31

Ministry of Health

Dr N M Goodman has been appointed a deputy chief medical officer of the Ministry

Dr Goodman was educated at Mill Hill and went from Sandhurst to the Worcestershire Regiment, with which he served in France, Belgium, and Germany Demobilised with the rank of captain, he went to Pembroke College, Cambridge, and the London Hospital, and after qualifying in 1923 spent eight years in general practice In 1934, after taking the D P H, he joined the staff of the Ministry of Health From 1937 to 1944 he was the British delegate on the Permanent Committee of the Office International d'Hygiène publique and a member of the health committee of the League of Nations In 1945 he was appointed deputy director of Health for Europe for UNRRA Two years later he became director of field services of W H O, and in 1948 assistant director-general of W H O In 1949 he rejoined the staff of the Ministry In 1955 he became the principal medical officer particularly concerned with the hospital and local authority services of the four Metropolitan regions Dr Goodman has been on official missions to most of the countries in Europe, and to U S A and Ethiopia, and was the Arris and Gale lecturer at the Royal College of Surgeons in 1941 He was elected F R C P in 1950 His book on *International Health Organisations and their Work* was published in 1952

Association for the Study of Medical Education

The function and structure of the teaching hospital has been chosen as the theme of the conference which the Association is holding at the Royal College of Physicians of London, Pall Mall East, S W 1, on Dec 2 at 10 A M Sir Robert Platt, P R C P, will be in the chair, and Sir Russell Brain will open the conference

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Mr P H Jayes has been appointed civil consultant in plastic surgery to the Royal Air Force

On Saturday, Dec 10, at 2 30 P M, at Mapperley Hospital, Nottingham, the Sheffield Regional Psychiatric Association is to hold its inaugural meeting, when Prof E Stengel will speak on relationships between psychiatric classification, nomenclature, and diagnosis

Dr G Georgieff, of the Ethiopian Government Ministry of Health Anti-Epidemic Service, is appealing for 1959 issues of *The Lancet* Any reader who is able to help is asked to get in touch with Dr Julius S Prince, P O Box 1035, Addis Ababa, Ethiopia

At a meeting of the Medical Electronics Discussion Group on Friday, Dec 2, at 6 P M, at the Institute of Electrical Engineers, Savoy Place, London, W C 2, there will be a discussion on telemetering biological data The opening speakers will be Dr G H Byford and Dr K G Williams

A semipermanent exhibition will be held at the Institute of Dermatology, Lisle Street, London, W C 2, from Dec 1 to 27, by Dr B E D Cooke on bullous lesions affecting the oral mucosa

The Scientific Film Association (3, Belgrave Square, London, S W 1) is revising its records of medical films for a new edition of its guide, and would be pleased to receive details of any films not previously included

A Supplement 1957–1959 to H K Lewis's Medical, Scientific and Technical Library Catalogue is now available from P O Box 66, 136, Gower Street, W C 1, price to subscribers 5*s*, to others 10*s* 6*d*

Births, Marriages, Deaths

BIRTH

JACKSON —On Nov 11 at Central Middlesex Hospital to Eileen (née Greenwood) wife of John W Jackson F R C S, a daughter—Jane Elizabeth—a sister for Jennifer and Adam

DEATHS

PHILLIPS —On Nov 19 at the Duke of York Home Bradford James Phillips F R C S J P aged 86 years of 4 Marlborough Road Bradford 8 the very dearly loved husband of Rose Phillips and dear father of Jean Cremated at Nab Wood Crematorium Shipley on Nov 23

RATHBONE —On Nov 15 following a stroke Mary (May) Rathbone L M S S A F L S of The Poplars Westington Chipping Campden daughter of the late Theodore Rathbone J P of [illegible]

Diary of the Week

NOV 27 to DEC 3

Monday, 28th

POSTGRADUATE MEDICAL SCHOOL OF LONDON Ducane Road W 12
4 P M Dr J S Robson Renal Excretion of Water in Health and Disease
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
1 30 P M (Queen Charlotte's Hospital Goldhawk Road, W 6) Mr A L I Easton Surgical Complications of Pregnancy
MANCHESTER MEDICAL SOCIETY
9 P M (Medical School, University of Manchester) *General Practice* Prof R E Lane Doctor in Industry

Tuesday, 29th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S W 1
5 P M Dr K D Keele *Evolution of Clinical Methods in Medicine* (First of two FitzPatrick lectures)
ROYAL COLLEGE OF SURGEONS OF ENGLAND *Lincoln's Inn Fields, W C 2*
5 P M Mr H B Stallard Malignant Melanoma of the Choroid Treated with Radioactive Applicators
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of *Hygiene and Tropical Medicine*, Keppel Street, W C 1) Dr L E Glynn Auto Antibodies and Diseases of Connective Tissue
INSTITUTE OF CHILD HEALTH, THE HOSPITAL FOR SICK CHILDREN, Great Ormond Street, W C 1
5 30 P M Dr G A Neligan Physiological Measurements in Newborn Infants
INSTITUTE OF DERMATOLOGY, Lisle Street, W C 2
5 30 P M Dr C D Calnan Cutaneous Allergy
ST MARY'S HOSPITAL MEDICAL SCHOOL, W 2
5 P M (Wright-Fleming Institute) Mr *Philip Rhodes Fluid Balance* in Obstetrics
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W 1
5 30 P M Dr G F Swann Myelography
ROYAL STATISTICAL SOCIETY
5 30 P M (London School of Hygiene and Tropical Medicine) *Medical Section* Dr J M Tanner Biometrical Problems in Studies of Human Growth
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M (General Infirmary at Leeds) Sir Aubrey Lewis Evaluating Psychiatric Treatment.

Wednesday, 30th

UNIVERSITY OF LONDON
5 30 P M (Westminster Medical School, Horseferry Road, S W 1) Dr J J Bunim (Bethesda) Interrelationship of Collagen Diseases
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P M Dr Victor Wynn Electrolyte Metabolism
INSTITUTE OF DERMATOLOGY
5 30 P M Dr Henry Haber Cellular Nævi and Malignant Melanomata
INSTITUTE OF DISEASES OF THE CHEST Brompton S W 3
5 P M Dr Howard Nicholson Diffuse Interstitial Pulmonary Fibrosis
INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
2 P M (Chelsea Hospital for Women Dovehouse Street, S W 3) Dr Robert Newton Pouch of Douglas
ROYAL INSTITUTE OF *PUBLIC HEALTH* AND *HYGIENE*, 28 *Portland Place*, W 1
3 30 P M Dr J P Bull Problem of Domestic Burning Accidents
MANCHESTER MEDICAL SOCIETY
4 30 P M (*Medical School University of Manchester*) Dr M I Grossman Gastro-œsophageal Reflux

Thursday, 1st

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P M Dr K D Keele Evolution of Clinical Methods in Medicine (Second of two FitzPatrick lectures)
ROYAL *COLLEGE OF SURGEONS OF ENGLAND*
5 30 P M Mr J B Pennybacker Acoustic Neuroma
ROYAL SOCIETY OF MEDICINE 1 Wimpole Street W 1
8 P M *Neurology* Mr F J Gillingham Mr Ian McCaul Mr John Hankinson Stereotaxic Surgery in Neurological Disease
BRITISH POSTGRADUATE MEDICAL FEDERATION
5 30 P M (London School of Hygiene and Tropical Medicine) Dr Bernard Lennox Nuclear Sexing and Human Chromosomal Anomalies
ST MARY'S HOSPITAL MEDICAL SCHOOL
5 P M (Wright Fleming Institute) Prof R W Scarff Proliferative Lesions of the Breast (Kettle lecture)
NUFFIELD ORTHOPÆDIC CENTRE WINGFIELD MORRIS ORTHOPÆDIC HOSPITAL, OXFORD
8 30 P M Mr Geoffrey Platt Arthroplasty of the Knee
UNIVERSITY OF ST ANDREWS
5 P M (*Physiology Department Queen's College,* Dundee) Sir Eric Riches Carcinoma of the Bladder

Friday, 2nd

ROYAL SOCIETY OF MEDICINE
10 30 A M *Otology* Mr Pennybacker Mr J D F Davies Intracranial Complications of Otogenic Origin
2 30 P M *Laryngology Prof R S Illingworth* Mr René Thomas Dr W J E McKee Is Removal of Tonsils and Adenoids Necessary?
5 30 P M *Anæsthetics* Prof R J Woolmer Information [illegible] (Presidential address)
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A M Mr A I Forrest Hypophysectomy in the Management of Patients with Malignant Disease
4 P M Prof G A Smart Spectrum of Thyroiditis
SOCIETY OF APOTHECARIES OF LONDON Black Friars Lane E C 4
5 30 P M *Medicine and Pharmacy* Dr A H T Robb-Smith Growth of Knowledge of Function of Blood
HARVEIAN SOCIETY
4 15 P M (Wellcome Foundation Euston Road N W 1) Dr [illegible] Broadened Spectrum of S[illegible] Syndrome and its Pathogenetic Implications (Hebe[illegible] oration)

Saturday 3rd

MIDLAND THORACIC SOCIETY
3 P M (Birmingham Medical Institute, 36, Harborne Road, [illegible] Birmingham 15) Dr D A Heath Hypertensive Pulmonary [illegible] Disease

The Lancet · Saturday 3 December 1960

GASTRECTOMY AND THE BLIND-LOOP SYNDROME

V J Kinsella
M D Sydney, F R C S , F R A C S
HONORARY SURGEON
W B Hennessy
M B Sydney, M R C P , M R A C P
CLINICAL ASSISTANT
GASTROENTEROLOGY UNIT, ST VINCENT'S HOSPITAL, SYDNEY

There are patients whose health has been ruined by intestinal malabsorption following gastrectomy for peptic ulcer Physicians and surgeons have pondered this problem for many years, but it is our belief that they have placed the emphasis on the wrong part of the complex pattern of causes Consequently, methods aimed at prevention have been inept, and the toll of unnecessary tragedies continues

Hurst (1913, 1929) was the first to describe the diarrhœa, and other symptoms later called " dumping " He stated that a large stoma permits precipitate emptying, and thus causes symptoms This became the accepted view But the surgeons said that a generous stoma was one of the requisites for the success of a gastroenterostomy Thus, Eusterman and Balfour (1936) advised that the stoma should include the whole width of the posterior wall of the stomach, from the lesser curvature, downwards and to the left, to the greater curvature at its most dependent point These authors stressed, as also did Moynihan (1926), that failure is often due to inadequate drainage through a stoma which is too small or too high

We thus find the large stoma stigmatised as a cause of failure, yet advocated as a condition of success

Further, Eusterman and Balfour wrote that " too rapid emptying of the stomach may cause a train of disturbances ", but, " from the roentgenographic standpoint, all resected stomachs appear to empty rapidly, yet few of the patients complain of any discomfort " Later, Custer, Butt, and Waugh (1946), also from the Mayo Clinic, expressed themselves as similarly puzzled by the fact that all patients show rapid emptying into the efferent loop, but only a few experience dumping

Moynihan (1926) also described this " too rapid emptying of the stomach " and the diarrhœa, which " may be slight, or may be so serious, so constant, uncontrollable and exhausting as to be the immediate cause of death " He concluded that " no adequate explanation of the complication can be given "

Today, the question is still confused The main emphasis is still placed upon too-rapid emptying, or loss of " hopper function " of the stomach The food is said to pass down the intestine in advance of the bile and pancreatic juice, thus establishing a " pancreatic-cibal asynchrony " (Royal Society of Medicine 1959, Herrington et al 1959)

Influenced by this hypothesis, surgeons had retained more, or even all, of the stomach, adding vagotomy, some have anastomosed the afferent loop to the greater curvature of the stomach, even adding a deliberate obstruction of the efferent loop at the lesser curvature

Hypotheses can be salutary, but only if they are valid And they are valid only if they can explain the facts

We therefore present a summary of the facts, firstly, those already well known, secondly, brief case-records of patients recently seen in our own practice

The Facts

Fluoroscopy shows that normally the duodenum and first loop of jejunum empty so rapidly that the movement can scarcely be followed by the eye The movement becomes slower as it passes downwards, so that the ileum retains its contents for some hours The " asynchrony " between the discharge of biliary-pancreatic secretions into the duodenum and the discharge of food through the gastrojejunal stoma is normally a few seconds or less, and is so short that it cannot prevent adequate mixing In practice, however, the " asynchrony " can be increased by obstruction in the afferent loop, and then becomes a serious factor But even then the "asynchrony" and "loss of hopper function " are not the primary and essential factors, for it is the obstruction which is the basic cause

Dumping and diarrhœa were first described as results of gastroenterostomy, not of gastrectomy

Results of gastroenterostomy are not better, but worse, with a small or high stoma

After vagotomy, the paradox may arise of delayed emptying of the upper part of the alimentary tract, together with diarrhœa

Conservative operations—antrectomy or gastroenterostomy, with vagotomy—are still followed by " the dumping syndrome " and severe weight loss (Everson et al 1947)

In four patients out of five, conversion of a Billroth-II to a Billroth-I gastrectomy will cure severe dumping symptoms

In a fifth patient, this conversion may fail

Dumping symptoms and diarrhœa after a Billroth-II operation may be cured by lifting up and supporting the afferent loop (Mimpress and Birt 1948, Capper and Butler 1951), or by Braun anastomosis between afferent and efferent loops (Schofield and Anderson 1953), or by the " pantaloon " anastomosis of Steinberg (1955)

Dumping symptoms and diarrhœa may follow total gastrectomy, but we have observed patients five, seven, and ten years after total gastrectomy with no gastrointestinal symptoms

In a series of patients after the Billroth-II operation, all may show rapid emptying into the efferent loop, but only a few of these may experience symptoms

Precipitate emptying of gastric contents into the afferent loop may be associated with dumping symptoms, but patients with dumping symptoms may show no emptying into the afferent loop (Goligher and Riley 1952)

After the Billroth-I operation, dumping symptoms and diarrhœa are less frequent and severe than after the Billroth-II

Historically, the great masters who fashioned the details of the Billroth-II methods (Mikulicz, Eiselsberg, Kronlein, Reichel, Polya, Hofmeister, and Finsterer) pointed to the importance of placing the afferent loop to the lesser curvature, because the reverse placement encouraged retrograde filling and this was to be avoided In their careful and prolonged follow-up of thousands of patients, the dumping syndrome was not a major problem

More recently, a few surgeons have placed the afferent loop to the greater curvature (*anastomose inversée*), and

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have even contrived a minor obstruction of the efferent loop at the lesser curvature In Australia, gastrectomy by this technique has not been successful, and vagotomy, with drainage operations, has been preferred American clinics have not presented a late follow-up after *anastomose intersee* A few brief references in the recent literature have mentioned the method only to condemn it (Muller 1956, Koto 1958)

Some Case-records

Case 1—Aged 47 In 1954, had a Billroth-II operation for duodenal ulcer This was followed by vomiting and diarrhœa In 1958, a hernia of small intestine through the mesocolon was repaired, followed in three weeks by separation of adhesion, and cholecystectomy for gallstones Vomiting began, diarrhœa and weight-loss became more severe, and the patient was transferred from the country to St Vincent's Hospital on April 15, 1959, suffering from severe malnutrition and steatorrhœa He also had advanced rheumatoid arthritis Barium meal showed gross delay in the emptying of his gastric remnant, and of the upper jejunal coils (fig 1) Under medical treatment, his vomiting ceased, and his condition improved But eight weeks after admission to hospital, he passed blood in the urine and was found to have a carcinoma of the bladder from which he succumbed

Fig 1—Case 1 Delay in emptying of gastric remnant and upper jejunal coils

Case 2—Aged 43 In 1958 had a Billroth-II operation, performed elsewhere, for gastric ulcer Soon after she began to vomit, lose weight and suffer from diarrhœa, and she was seen in consultation by one of us (W B H) She had wasting and widespread œdema, ascites, steatorrhœa, and severe hypoproteinæmia Barium meal showed a large dilated afferent jejunal loop which still contained barium seventeen hours after the meal (fig 2) Fluoroscopy showed that the stomach emptied into the afferent loop, and this emptied back into the stomach, so that a pendulum movement resulted At laparotomy, performed elsewhere on Sept 1, 1959, a thickened, writhing, dilated afferent loop was seen, and dark foul-smelling fluid poured from this when the stoma was opened in an attempt at reconstruction Gastric and colonic fistulæ resulted, and, in spite of two further laparotomies, the patient died on Oct 18, 1959

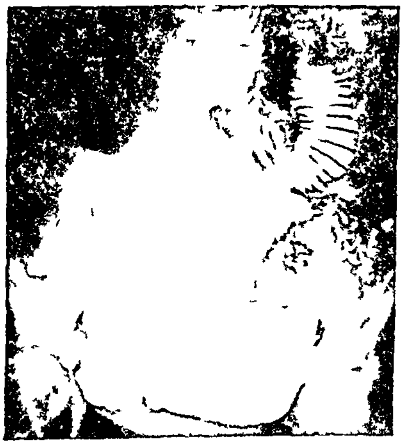

Fig 2—Case 2 Barium retained in dilated afferent jejunal loop seventeen hours after meal

Case 3—Aged 50 Had partial gastrectomy for duodenal ulcer in January, 1957, reoperation for gastrocolic fistula in August, 1958, vagotomy in December, 1958, for an ulcer in the efferent jejunal loop At the last operation, the pancreas was reported to be normal In 1959, she was seen by us, and was admitted She had diarrhœa, severe malnutrition, weight loss (from 10 st 4 lb to 6 st 4 lb), gross œdema of the lower limbs, and dry thin scaly skin with large ecchymoses Investigations revealed gross steatorrhœa and hypoproteinæmia Perhaps this, as well as altered pH in the intestine, contributed to the diarrhœa Radiographs showed consistent *filling and dilatation of the afferent jejunal loop (fig 3)* Her response to intensive therapy was only partial and temporary, and she died on Dec 11, 1959 Necropsy findings included a stomal ulcer, a grossly dilated afferent jejunal loop, enteritis, and several non-beta-cell pancreatic microadenomata (Among patients with these tumours, a few suffer from diarrhœa, and most of them have had a constriction of the duodenum in its distal parts, or the jejunum, either by the pancreatic tumour or by a jejunal ulcer)

Fig 3—Case 3 Dilatation of afferent jejunal loop

Case 4—Aged 50, had had gastroenterostomy in 1917, for gastric ulcer, followed one week later by reoperation for vomiting On account of repeated *hæmorrhages*, partial gastrectomy was performed elsewhere, in 1951 About six weeks later, diarrhœa began and continued, with 6 to 25 bowel actions daily Her appetite remained excellent, but, in spite of frequent big meals, her weight fell from 7 st 2 lb to 6 st 5 lb, and investigations revealed gross steatorrhœa Barium meal in 1959 showed barium passing back into the afferent loop, but stopping abruptly, as though obstructed, an inch or two proximal to the stoma (fig 4) At about this time, the patient bled per vaginam A carcinoma of the cervix was discovered for which she is still under treatment

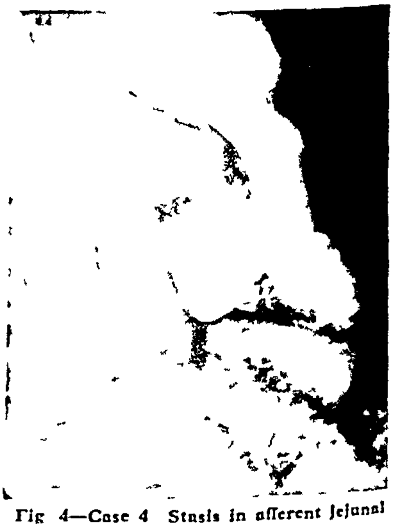

Fig 4—Case 4 Stasis in afferent jejunal loop

Case 5—Aged 50, had diarrhœa and weight-loss after Billroth-II gastrectomy A barium meal showed a picture similar to fig 4

Case 6—Aged 42 Had had a partial gastrectomy, with *anastomose intersée* five years previously for duodenal ulcer She was reasonably well for two to three years Then she began to get attacks of fullness after eating, with copious brown vomiting, diarrhœa, and weight loss. Intermittent spontaneous improvement would occur. Barium meal showed a dilated afferent loop. She was referred for opinion by her physician and we advised reoperation.

Case 7.—Aged 55. In 1952, had cholecystectomy for gallstones, later a choledochoduodenostomy and sphincterotomy. But the pains persisted. In 1957 she had a partial gastrectomy performed elsewhere for a small gastric ulcer. Her pains disappeared, but diarrhœa began—4 or 5 large yellow offensive motions a day—and she lost 28 lb. in two years. Investigation revealed gross steatorrhœa. Barium meal showed a gastrectomy of adequate extent, but barium passed back into the afferent loop and stopped completely about one inch from the stoma (fig. 5). A cholecystogram showed an unusual accumulation of dye in the duodenum with delayed emptying, and the duodenum appeared wider than in the pregastrectomy barium meal. On Feb. 2, 1959, at laparotomy, the liver was found adherent to afferent loop and stoma. It was felt that a freeing of this would be only temporarily effective, so a short anastomosis was made between the second part of the duodenum near the ampulla and an upper jejunal loop. After operation the diarrhœa ceased, and the motions have remained normal, and she has gained over 14 lb. in the nine months since operation.

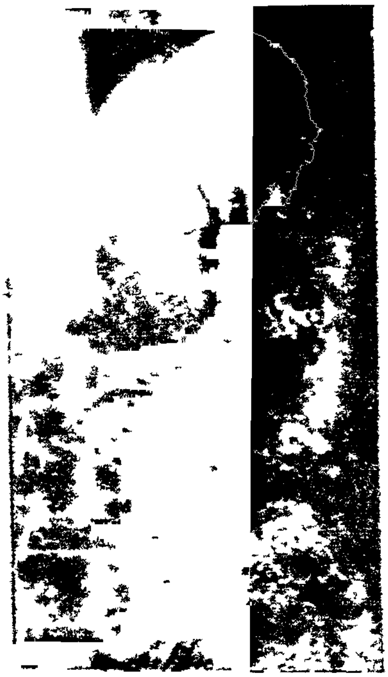

Fig. 5—Case 7: Stasis in afferent jejunal loop.

Explanation of the Facts

It is evident from these cases that "dumping" symptoms and diarrhœa are not primarily and essentially caused by (1) altered time-relationships with failure to mix, (2) large stoma, (3) loss of this or that function of stomach, (4) loss of hopper function, (5) loss of digestive secretions, or (6) precipitate emptying into the efferent loop. The symptoms can occur in the absence of any one of these factors—e.g., (a) even with the small stoma of an œsophagojejunostomy, (b) with the stomach still retaining its secretory functions after gastroenterostomy, (c) with the reservoir function still intact, and even exaggerated after vagotomy, and (d) with ample, and even exaggerated, opportunities for the mixing of food and pancreatic secretion, as in cases 1, 2, 3, and 6. Moreover, a patient may remain free from digestive symptoms even after total gastrectomy.

The only common factor in the above patients, and, therefore, the primary and essential one, is stasis in the duodenojejunal loop. In two of the patients (cases 2 and 7) fluid was removed from the afferent loop during operation, and culture revealed a mixed bacterial flora. These patients had previously improved under treatment with broad-spectrum antibiotics. Stasis in lower intestinal loops is already well known as a cause of malabsorption—the "blind-loop syndrome". If its importance is also recognised in the uppermost loop, the duodenojejunal, then an important piece falls into place in the puzzle of the postgastrectomy syndrome.

To achieve a permanently good result after Billroth-II gastrectomy, stasis in the afferent loop must be avoided. Symptoms may improve or disappear during the first twelve months after operation, because the congestion and rigidity in healing tissues, especially if subjected to low-grade infection, may take twelve months to disappear, as can easily be observed in the scar on the abdominal wall. Conversion of a Billroth-II operation to a Billroth-I, and anastomoses between afferent and efferent loops, and suspension operations on the afferent loop cure symptoms, because there has been some degree of afferent-loop obstruction. Sometimes the conversion to a Billroth-I operation fails, perhaps because of some degree of jejunal obstruction at the site of repair of a distorted and thickened jejunal loop. Other factors may also operate. Vagotomy causes stasis in the stomach and first part of the intestinal tract. A Billroth-I operation involves a considerable degree of vagotomy, and it diminishes secretion.

Stasis in the duodenojejunal loop may therefore be caused by (1) mechanical obstruction, (2) a to-and-fro emptying between the afferent loop and the stomach, and (3) vagotomy.

Effect of Afferent-loop Obstruction

Obstruction of the afferent loop may produce several groups of symptoms:

1.—Epigastric pain or discomfort, worse after meals.

2.—Widespread autonomic reflex effects, and internal and external secretory disturbances of the liver and pancreas.

3.—Intermittent copious vomiting of bile.

These three groups have been well recognised, but we would add a fourth. It is our opinion that malabsorption, with its diarrhœa, anæmia, and nutritional disturbances, must also be added to the symptoms caused by afferent-loop stasis. This has not been widely recognised. Indeed Card disagrees on the grounds that this part of the gut is "extremely active and empties itself readily". But he pays an undeserved compliment to the surgeon in supposing that the local intestinal order always remains exactly the same after operation (Royal Society of Medicine 1959). The afferent loop is not a blind loop, unless the surgeon makes it so.

Radiological Diagnosis of Afferent-loop Stasis

After a properly constructed gastrectomy, the opaque meal should pass easily and freely into the efferent jejunal loop. The afferent loop should show, at most, a slight trickle of barium gradually tailing off before the second part of the duodenum is reached, just enough to show that there is neither obstruction at the critical point near the lesser curvature, nor any dilatation of the loop (fig. 6).

Patients suffering from afferent-loop stasis fall into three radiological groups:

1.—There may be no radiological signs, because the stasis is caused by obstruction at the point where the afferent loop meets the stomach, and barium is therefore prevented from entering the obstructed loop.

2.—In some patients the obstruction is at a point away from the stoma, and this is shown when the barium passes freely back into the afferent loop for one or two inches and then stops abruptly.

3.—In other patients, the stasis is caused by free retrograde emptying of the stomach into the afferent loop and then emptying of the afferent loop into the stomach, so that a pendulum movement results.

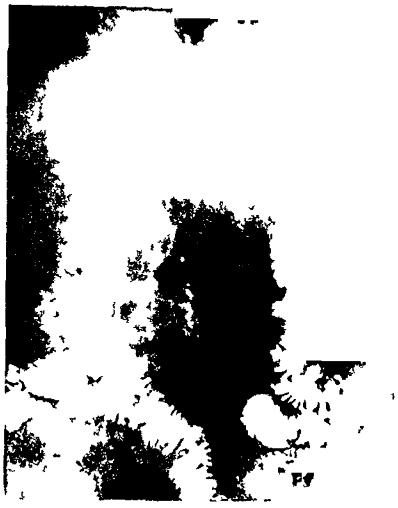

Fig 6—Ideal radiographic appearance after gastrectomy

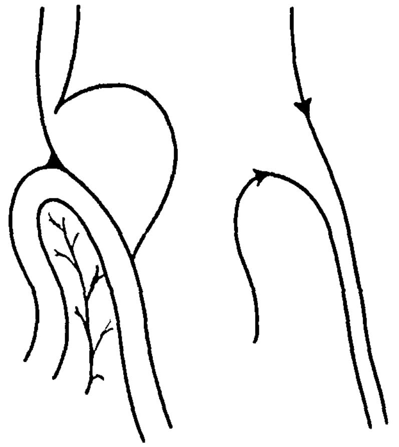

Fig 7—The first principle in Billroth-II reconstruction—the quiet confluence of unobstructed streams

Non-filling of the afferent loop may, therefore, be associated with a perfectly constructed anastomosis, or with a seriously obstructed loop If the patient suffers from malabsorption, it is advisable to do a choledochogram in the hope that the duodenum may be seen on the radiograph

Causes of Malabsorption

It is our view that emphasis should be shifted from precipitate gastric emptying to stasis in the afferent loop, as a cause of malabsorption after gastrectomy Other causes which may contribute include pancreatitis, and perhaps defects in the intestinal mucosa

First Surgical Principle of Prevention

A first principle of gastrointestinal surgery, which must be rigorously applied in gastric surgery, is that an end-to-side anastomosis must achieve a *quiet confluence of unobstructed streams*

This means, among other things, that the anastomosis must be " en-Y ", whether between stomach and intestine, or between two loops of intestine The old masters wrought well There is no place for anastomosis " en-T ", still less for the emptying of one viscus at an acute angle against the stream of the other (the *anastomose inversée*) Such junctions effect a turbulence rather than a confluence They are avoided by Nature, in the rivers, in plants, and in the animal body They cause an increased mechanical stress, and an accelerated mechanical destruction But over and above this, in the digestive tract they interfere with local functions by unduly prolonging the digestive phase in part of the bowel Increased functional stress, disturbance of bacterial flora, and inflammation are the invariable accompaniment of stasis in a hollow viscus

For years, one of us has made every effort to apply this principle in the surgical treatment of the afferent loop, and our series of gastrectomies for ulcer, numbering nearly four hundred, has not been complicated by diarrhœa and malabsorption Figs 6 and 7 show the ideal to be aimed at

Detailed Application of this Principle

The afferent loop must be placed to the lesser curvature

It must not be too long If slightly too long, it may kink If grossly too long, it may also allow the passage behind it of another intestinal coil It must not be too short, for obvious reasons

At the uppermost point of the loop, where it turns downwards to meet the lesser curvature, there is a tendency to kinking which must be prevented by lifting the antimesenteric border away from the mesenteric border, by suspending it to the lesser curvature of the stomach above the stoma This is done by means of the Kapeller suspension stitches These must be so applied that torsion is not produced by, for example, fixing the apex of the jejunal loop in front of the lesser curvature The stitch should take up the anterior surface of the stomach, just in front of the lesser curvature, then the posterior surface just behind it, then the posterior surface of the jejunum just behind its greatest convexity, and then its anterior surface just in front

The incision in the stomach must pass downwards and to the left, so that the stoma and the efferent loop are continued in the one staight line down to and away from the greater curvature If too much of the greater curvature is removed, obstruction is caused by Visick's " question-mark deformity "

The incision in the jejunum must be placed accurately on the antimesenteric border, and not obliquely, otherwise torsion results

The handling and suturing of the visceral walls must be refined and delicate, to avoid excessive " anastomositis " with its scarring and fixed mucosa The niceties of suturing have been described earlier (Kinsella 1959)

In retrocolic anastomoses, the mesocolon must be so sutured that kinking of the jejunum is avoided

In antecolic anastomoses, the omentum must be placed so as to prevent adhesion of the afferent and efferent loops to each other, or to the parietal incision

Conclusion

It is our opinion that malabsorption following gastrectomy could be largely prevented, and some sufferers could be salvaged, by the application of the principles described in this paper Gastrectomy is a precision operation The solution of the problem of its complications lies in perfecting the technique of the operation as it is applied, not in the devising of new combination operations, which involve the same old dangers, and add new ones of their own Vagotomy adds gastric retention, necessitating a considerable number of re-operations (even when a primary drainage operation has already been done), mediastinitis, hæmorrhage from paraœsophageal tissue and from spleen (Herrington et al 1959), and, if by the thoracic route, all the complications peculiar to thoracotomy

The emphasis in gastrointestinal surgery should not be placed upon precipitate emptying as a disease factor It is not this which is to be feared, but rather stasis—and stasis is technically avoidable

Summary

Malabsorption after gastrectomy is often due to stasis in the afferent duodenal-jejunal loop, and is an example of " the blind-loop syndrome "

The causes of afferent-loop stasis are discussed, and the technical details of avoiding it are described

Radiological diagnosis of afferent-loop stasis is discussed.

A first principle of gastrointestinal surgery is the *quiet confluence of unobstructed streams*

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EARLY POSTOPERATIVE INFLAMMATION OF THE EFFERENT LOOP AFTER POLYA GASTRECTOMY

F. I. TOVEY
M.B. Brist., F.R.C.S.
SURGEON-IN-CHARGE, MEN'S DEPARTMENT,
MARY CALVERT HOLDSWORTH MEMORIAL HOSPITAL,
MYSORE CITY, SOUTH INDIA

This article reports three cases of early postoperative inflammation of the efferent loop of the jejunum following a Polya-type gastrectomy. The operative procedure was almost identical in the three cases. About five-sixths to six-sevenths of the stomach was removed. A new lesser curve was constructed by suturing the right end of the divided stomach remnant, leaving a large enough opening for a $1^1/_2$–2 in. stoma at the greater curve end. This was anastomosed to an antecolic loop of the jejunum, the afferent loop being short and related to the greater curve, and the efferent loop being related to the newly constructed lesser curve (fig. 1). Light uncovered clamps, as recommended by Burge (1956), were used and were applied to the jejunum, keeping well away from the mesentery.

The lesser curve was supported by leaving the ligature around the left gastric artery long, and by tying it to the last suture used to attach the jejunum to the re-formed lesser curve of the stomach (fig. 2) as advised by Capper and Butler (1951) and Butler and Capper (1951). In the first patient, most of the re-formed lesser curve was covered up by suturing the first inch or so of the efferent loop to it, but in the others it was left uncovered.

In each of these cases, something had obviously gone wrong on about the fourth postoperative day. In the first two, at first, there seemed to be insufficient reason for reopening and when an operation became imperative, their condition had deteriorated so rapidly that intervention was too late. It was this experience that led to a laparotomy being done on the third patient as soon as something amiss was suspected; this patient survived.

THE FIRST PATIENT

A man, aged 26. Had been admitted three weeks before operation with an attack of severe upper-abdominal pain which was first thought to be biliary colic but was later diagnosed as due to a leaking duodenal ulcer. He was a very tensed-up artistic type of young man. A gastrectomy was done on April 12, 1951, six-sevenths of the stomach being removed. There was extensive duodenal scarring with fresh adhesions to the gallbladder and liver. The duodenum was divided, closed $1^1/_2$ in. beyond the pylorus, and a drain was placed down to the stump. After the operation he had much trouble with wind, and the stoma did not work well until the fourth day, when he had a bowel action. He continued to have some colicky pain relieved by enemas on April 20. His pain became more constant and on April 21 he had sudden severe pain with shock and sweating. A diagnosis of a perforation was made, a laparotomy was done, and the first 18 in. of jejunum was found to be intensely inflamed and of tissue-paper consistence. There was a series of ulcers, three of which had sloughed and perforated. The perforations were oversewn and a free omental graft was applied. The patient did not rally and died about six hours after the operation. A post-mortem examination confirmed the ulceration of the jejunum. The stomach and duodenal suture lines were sound. The patient was not given any chemotherapy after operation.

THE SECOND PATIENT

A man, aged 24, gave a history of four years' epigastric pain, which was shown to be due to a duodenal ulcer. On July 11, 1958, gastrectomy was performed, five-sixths of the stomach being removed. The duodenal ulcer was posterior with scarring but was not too adherent. A duodenal closure was done. The anastomosis was completed as described (figs. 1 and 2), and 500 000 units penicillin and 1 g. of streptomycin in 5 ml. saline were put into the peritoneal cavity before closure. The postoperative progress was normal until the night of July 13, when he had an attack of dyspnœa which the house-surgeon thought was due to asthma. On the morning of July 14 he seemed a little unwell and had abdominal distension. There was no rise in the pulse-rate or temperature. A vertical X-ray film of the abdomen showed fluid levels in the small bowel, and gas in a loop in the left hypochondrium which was thought to be the splenic flexure of the colon. By 4 P.M., he had had three motions, but the abdomen was still a little distended and was silent.

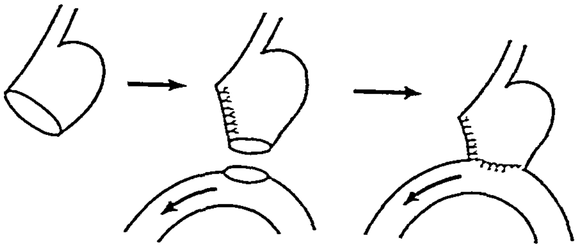

Fig. 1—Afferent and efferent loops in Polya gastrectomy.

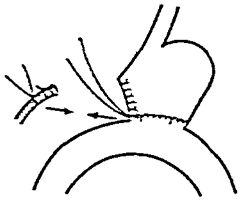

Fig. 2—Suspension of lesser curve of stomach after Polya gastrectomy.

An X-ray at 7 P.M. showed fewer fluid levels in the small intestine, and more gas in the splenic flexure. On July 15 he had six motions, the abdomen was softer and only a little distended. On July 16, the diarrhœa was less. His temperature was about 100° F, and his pulse-rate 90–100. On July 17 he had five motions and on the next day the diarrhœa continued and his temperature rose to 102°–103°F. He developed a widespread bronchopneumonia confirmed by X-ray. The abdomen became distended and an X-ray showed no fluid levels but gas in the left colon with a superimposed distended loop of small bowel in the left hypochondrium. Next day the abdomen was even more distended though peristalsis was still present. At midday he had a small vomit of clear fluid and his condition deteriorated. A Levin tube was passed but only a little clear fluid was aspirated. An X-ray of the abdomen now showed only a distended loop in the left hypochondrium, which looked as if it was small bowel.

A laparotomy was performed through the previous incision.

The proximal 2 ft. of jejunum were grossly distended and inflamed, but not obstructed. There were four sloughs about 1 ft. from the duodenojejunal flexure, the longest of which ruptured as the loop was delivered. One, about 9 in. lower down, had already burst and spilled into the peritoneum. All sloughs and perforations were oversewn, or closed with two layers of interrupted thread. The distended upper part of the jejunum was decompressed with a Bruecke double-lumen tube, introduced through a stab-incision in healthy bowel wall which was closed with a purse-string suture. The rest of the small intestine was of normal size. The duodenal and stomach suture lines were healthy. 500,000 units of penicillin and 1 g. of streptomycin were left in the peritoneal cavity, and a suprapubic peritoneal drain was inserted. His condition was fairly satisfactory after operation, but he died at 2.30 A.M. on July 20. Penicillin 500,000 units and streptomycin 1 g. were given twice daily intramuscularly from July 14 to July 16. On July 18, penicillin 100,000 units and streptomycin 1 g. twice daily intramuscularly was begun. Permission could not be obtained for postmortem examination.

THE THIRD PATIENT

A man, aged 18, gave a history of twenty days' epigastric pain before admission. He was found to have a duodenal ulcer. After two weeks' medical treatment, he still required morphine injections for pain. A gastrectomy was performed on Aug. 14, 1958, when five-sixths of the stomach was removed. A chronic duodenal ulcer was found penetrating the pancreas posteriorly, and puckering the anterior wall of the duodenum. A prepyloric closure was done. 500,000 units penicillin and 1 g. of streptomycin were left in the peritoneal cavity before closure. Next day, he appeared well and a few bowel sounds were present. On the morning of Aug. 16, he passed flatus, but bowel sounds were absent and his abdomen was slightly distended. Small amounts of clear fluid were being aspirated from the Levine tube. At 5.30 P.M., he was more distended with occasional bowel sounds. He passed no flatus after a flatus tube was inserted. A vertical X-ray showed distended loops of small intestine with gas in the colon. He passed much flatus after a turpentine enema. A further vertical X-ray showed distended loops still present, and gas in the colon. At 9.30 P.M., though still distended, he passed more flatus, and had vigorous peristalsis.

Next day, Aug. 17, there was still vigorous peristalsis, and some lower abdominal distension. A considerable amount of greenish fluid was now being aspirated. An enema gave a good result, and the distension of the lower part of the abdomen disappeared. A vertical X-ray of abdomen showed a distended loop of bowel in the left hypochondrium, superimposed on a distended colon. The radiological appearances resembled those of the previous patient (case 2).

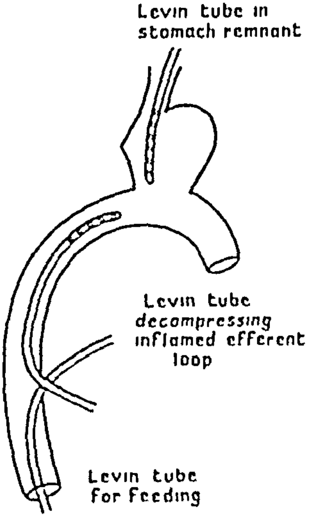
Levin tube in stomach remnant
Levin tube decompressing inflamed efferent loop
Levin tube for feeding

Fig. 3—Case 3. Position of Levin tubes after operation for inflammation of efferent loop.

A tentative diagnosis of inflamed, distended efferent loop was made, and the abdomen reopened. The proximal 18 to 21 in. of the efferent loop were intensely inflamed and distended, and showed multiple ulcers which had not yet sloughed. The bowel wall was very friable. An opening was made into the jejunum below the inflamed area, and the bowel was decompressed with a Bruecke double-lumen tube. One Levin tube was then passed through the opening into the inflamed proximal bowel, and one a long way downwards along the distal jejunum (which appeared normal). The opening was closed with a purse-string suture. The bowel wall was then sewn over both tubes, as in a Witzel jejunostomy. The tubes were brought out separately through stab-wounds, and the loop was attached by a few sutures to the adjacent abdominal wall. 500,000 units of penicillin and 1 g. of streptomycin in saline were left in the peritoneal cavity. After operation, hourly aspiration was applied to a Levin tube in the stomach, and continuous suction to the Levin tube in the proximal part of the efferent loop. The tube into the distal part of the efferent loop was spigoted, and the patient was given parenteral fluids and electrolytes.

After two days, $^{1}/_{2}$ oz. plain water was administered hourly by the distal tube. By Aug. 23, this had been increased to 6 pints of half-strength milk in 0.3 N saline per twenty-four hours, given by continuous drip, with added potassium chloride 4.5 g. daily. The bile aspirated from the proximal tube was filtered, boiled, and returned through the distal tube to the bowel. On Aug. 24, the proximal tube was removed from the efferent loop. Feeding by mouth was increased, and feeding through the distal tube was decreased daily. The distal Levin tube was withdrawn on Aug. 29. Thereafter, he was given soft solids and gradually progressed to a normal diet. The fistulæ from which the tubes had been withdrawn healed quickly. The Levin tube in the stomach had been withdrawn earlier on Aug. 25.

Discussion

The appearance of the affected loop of jejunum in these cases was similar to that of a localised necrotising enteritis. It also bore some resemblance to the appearance of the bowel after a mesenteric thrombosis. This possibility was not thought of until recently, and no note was made at operation about the arterial supply to the affected segments, though venous congestion was seen in all the cases. We have had a recent case of mesenteric thrombosis in a patient with Buerger's disease, and we were surprised at the similarity in appearance, though the segment involved was much longer. The resemblance of these cases to those reported by Watson (1958), with distension of the afferent loop, is interesting.

The operative procedure adopted in the third case was successful. Resection of the affected loop would have been very difficult in all these patients because of the upward retraction of the stomach, the uncertain upper demarcation of the segment involved, and the intense inflammatory reaction. Once necrotic ulcers have developed, or perforation has occurred, it is difficult to know whether any treatment other than resection would be successful. A plea is made for early laparotomy on all cases of Polya gastrectomy that show some definite departure from the normal course of recovery. A sudden change in wellbeing, an unexplained colicky abdominal pain, distension, and restlessness should be enough to arouse one's suspicions. Peristalsis may persist for some time, and there may be very little in the way of rigidity and guarding. The patient may be passing flatus, or even having loose motions. Abdominal distension and ileus occur much later when perforation has taken place and then it may be too late to do anything.

Summary

Three cases of early severe postoperative ulceration of the efferent jejunal loop after a Polya gastrectomy are described.

The clinical manifestations were a change in well-being, upper abdominal pain, some distension, and persisting peristalsis.

Decompression of the loop was successful in one case.

The cause of the condition is unknown and it is

suggested that it may be associated with necrotising enteritis

I must thank Mr W. M. Capper for permission to publish the details of the first patient, Mr Geoffrey Darke, who performed the first operation on this patient, and Mr Charles Bartlett, who came to my assistance at the time of the second operation.

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ASBESTOSIS AND ABDOMINAL NEOPLASMS

E. E. KEAL
M.R.C.P., D.C.H.
SENIOR REGISTRAR IN CHEST MEDICINE, LEEDS CHEST CLINIC, AND KILLINGBECK HOSPITAL, LEEDS, 14*

IN 1953, an impression was formed at The London Hospital that women suffering from pulmonary asbestosis had ovarian neoplasms more often than other women. The occurrence of further cases led to the present investigation, which is based on a search of the records of the hospital since 1948. In that period 23 women have been inpatients with a diagnosis of asbestosis. 15 are known to have died, 4 with lung cancers and 9 with intra-abdominal neoplasms. Of these 9, 1 had an ovarian carcinoma, and 4 had peritoneal growths, possibly of ovarian origin. In the other 4 the diagnosis was carcinomatosis peritonei and, though 2 underwent laparotomy and 1 came to necropsy, no primary lesion was found. During the same period, 19 men were admitted with asbestosis. 15 of them are known to have died, including 10 with lung cancer and 1 thought to have a malignant mesothelioma of peritoneum, though there were some features suggestive of a primary bronchial neoplasm. Detailed case-histories will be given only for the 9 women with ovarian or peritoneal growths, and for the one man thought to have a peritoneal mesothelioma. Relevant details of the other cases are summarised in tables I and II, and will be briefly discussed. Many other patients with asbestosis attend the hospital, but only as outpatients, and so do not appear in the diagnostic index. Their total numbers are therefore not known.

Case-records

Occupational histories are omitted for brevity, but will be found in tables I and II.

Case 1.—A spinster, aged 42, was admitted in May, 1951, with papilloedemic hypertension and left ventricular failure. A diagnosis of asbestosis had been accepted by the pneumoconiosis panel five years earlier and a full pension granted. While in hospital she had retention of urine, and pelvic examination revealed a swelling in the pouch of Douglas. A week later she suddenly became unconscious, with signs of a left hemiplegia, and she died shortly afterwards.

Necropsy.—Death was due to an embolus in the right carotid artery. There was no pleural effusion, but there was a narrow band of fibrous adhesions over the anteromedial surface of the

TABLE I—CASES OF ASBESTOSIS (WOMEN)

Case	London Hospital number	Present age or age at death	Years since first exposure	Duration of exposure (years)	Type of exposure	Associated disease
1	22415 50	Died 43	21	21	Asbestos grinding	Carcinoma of ovary
2	22152 49	Died 45	28	7	Asbestos spinning	Peritoneal carcinoma probably from ovary
3	51401 49	Died 60	46	4	Asbestos spinning	„ „ „ „
4	14678 52	Died 49	30	4½	Carding room	„ „ ? ovary ? mesothelioma
5	4709 53	Died 52	36	3	Mattress department	Carcinomatosis peritonei
6	15921 55	Died 54	38	2	Asbestos spinning	Peritoneal carcinoma probably from ovary
7	41550 47	Died 39	23	4	Slab-making department	Carcinomatosis peritonei
8	37260 55	Died 59	34	1	Slab-making department	„
9	50268	Died 35			Not known	„ „
10	17826 48	Died 66	15	1 month	Warping machine	Carcinoma of bronchus (squamous cell)
11	29339 52	Died 59	38	7	Asbestos grinding	„ „ (polygonal cell)
12	22367 53	Died 45	27	4	Asbestos weaving	„ „ „ atypical cells in sputum
13	21148 47	Died 50	20	20	Mattress department	„ „ (type not stated)
14	46720 49	43 (1951)	20	3	Asbestos spinning	Last seen 1951
15	16254 50	44 (1950)	25	3	Unspecified	Well 1950
16	53494 50	57	18	13	Unspecified	Well
17	10384 53	53	21	1½	Unspecified	Well
18	20073 54	51	26	6	Asbestos weaver	Congestive heart failure
19	20672 54	72	19	5	Sweeper in asbestos factory	Cholecystitis
20	24986 55	Died 52	33	3	Spinning department	Pulmonary hypertension, right heart failure, carcinoma of breast
21	14093	Died 63	30	3	Mattress filler	Carcinoma of stomach
22	25864	53	17	17	Pipe lagger	Carcinoma of breast
23	41545 51	59	32	4	Unspecified	Congestive heart-failure

TABLE II—CASES OF ASBESTOSIS (MEN)

Case	London Hospital number	Present age or age at death	Years since first exposure	Duration of exposure (years)	Type of exposure	Associated disease
24	27245 56	Died 50	26	23	Cleaning ventilators	Malignant mesothelioma of peritoneum
25	22429 51	Died 60	45	45	Asbestos lagger	Carcinoma of lung (anaplastic, spheroidal cell)
26	15204 53	Died 53	5	5	Asbestos grinder	„ „ (polygonal cell)
27	11207 59	Died 47	22	2	Sorter in asbestos factory	„ „ „ (anaplastic, spheroidal cell)
28	24877 56	Died 55	7	7	Tipping asbestos	„ „ „ (not stated)
29	38115 56	Died 65	6	6	Asbestos carter	„ „ (squamous cell)
30	29223 57	Died 54	30	15	“ Asbestos [illegible] ”	„ „ „ (squamous cell)
31	19585	Died 76	34	17	“ Asbestos factory ”	„ „ „ (squamous cell)
32	24926	Died 56	40	40	Boiler coverer	„ „ „ (squamous cell)
33	2613 56	Died 53	31	18	Unloading and sewing asbestos	„ „ (anaplastic, spheroidal cell)
34	42921	Died 37	18	18	Boiler coverer	„ „ „ (polygonal cell)
35	3719 48	Died 65	15	4½ mos	Asbestos grinder	Suppurative pneumonia, cerebral abscess
36	48234 40	56	42	42	Boiler coverer	Emphysema, congestive heart-failure
37	28817 50	Died 62	19	19	Asbestos packer	Bronchopneumonia, diabetes mellitus
38	2599 51	Died 60	40	7	Asbestos packer	Haematemesis from acute gastric erosion
39	5262 52	Died 60	24	4	Asbestos factory labourer	Calcific aortic stenosis
40	17399 55	49	35	6 mos	Breaking up asbestos	Bronchitis
41	12810	56	18	9	“ Asbestos factory ”	
42	23776 49	43 (1952)	25	25	Loading and blending asbestos	

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* This work was done while the author was medical registrar at The London Hospital, London, E.1

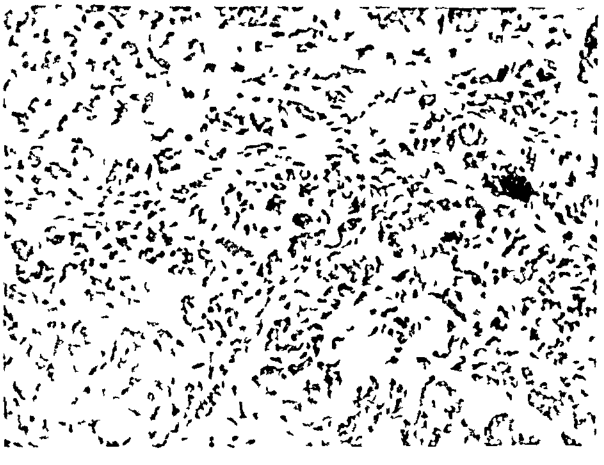

Fig 1—Case 1 Papillary, columnar, and cuboidal cell carcinoma, with occasional aggregates of larger, pale-staining polygonal cells suggestive of the whorling seen in squamous cell carcinoma (×110)

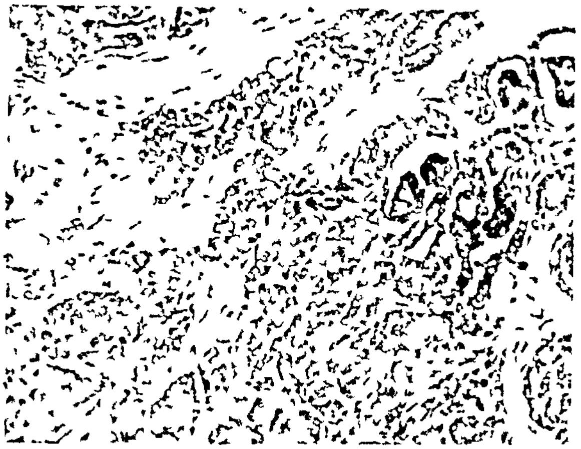

Fig 2—Case 2 Papillary, tubular, and solid masses of cuboidal cell carcinoma, suggesting an ovarian primary (×114)

right upper lobe All lobes of lung showed a firm shotty induration with almost confluent nodules of greyish-black fibrosis against a paler reddish-brown background The fibrosis was more diffuse in the anterior parts of the right upper lobe and in the right lower lobe, showing a blue-grey interlacing network of fibrous strands The left ovary was enlarged (11 cm diameter) by a nodular necrotic cystic carcinoma, unaccompanied by peritoneal or any other secondary deposits

Histology—The tumour was a papillary, columnar and cuboidal-cell carcinoma, with occasional aggregates of larger pale-staining polygonal cells suggestive of the whorling seen in squamous-cell carcinoma (fig 1) The lungs showed peribronchiolar and peribronchial interstitial fibrosis with some slight bronchiolar epithelial hyperplasia Numerous asbestos bodies were found, often entirely or partially ingested by giant-cells of the foreign-body type A few asbestos bodies were found in a partially fibrotic hilar lymph-node

Case 2—Asbestosis had been diagnosed at the age of 40 She was admitted when she was 45, with a history of lower abdominal bearing-down pains for one year, followed by anorexia, diarrhœa and weight-loss A large hard irregular mass was felt in the lower abdomen, arising from the pelvis At laparotomy, the whole of the posterior sheath of the rectus appeared infiltrated by growth and no further examination was made A biopsy was taken and histological examination showed a carcinoma composed of papillary, tubular, and cuboidal cells, suggesting an ovarian primary (fig 2) She died in hospital after nine months

Necropsy (Dr B E Heard at St Mary's Hospital)—There were many fibrous adhesions in both pleural sacs with numerous, evenly scattered, dark nodules throughout both lungs Scrapings showed asbestos bodies A great amount of growth filled the peritoneum and invaded the walls of the intestines, and the greater omentum There was one nodule in the liver The ovaries were not identified in the mass of growth filling the pelvis The cause of death was given as carcinoma in peritoneum, probably from ovary

Case 3—She was found to have asbestosis in 1953, and was admitted one year later at the age of 61, with a five-week history of abdominal distension, anorexia, constipation, and progressive weight-loss She was cachectic There was ascites, and a large hard irregular mass could be felt rising from the pelvis She required repeated paracentesis, and died after twelve weeks in hospital

Necropsy—Fibrous adhesions were found at the apex of the left lung There was conspicuous diffuse emphysema Asbestos bodies were seen in smears from the cut surface of the lung Fine fibrosis was present throughout both lungs with discrete areas of anthracosis, maximal in the lower lobes There were nodules of growth throughout the peritoneum, with plaques of growth surrounding the liver and spleen A mass of growth filled the pelvis and the ovaries were not identified On histological examination, the lungs showed variable pleural fibrosis Numerous asbestos bodies were seen, with patchy fibrosis in the lung-substance Sections of the tumour showed a moderately scirrhous solid trabecular small cell carcinoma, with grouping of the cells suggestive of rosettes (fig 3)

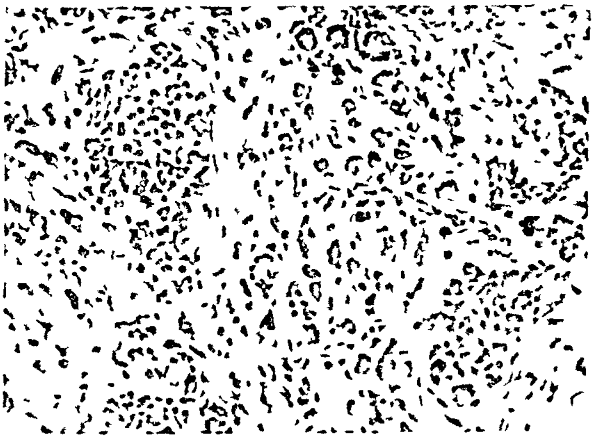

Fig 3—Case 3 Moderately scirrhous solid trabecular small polygonal-cell carcinoma with grouping of the cells suggestive of rosettes (×120)

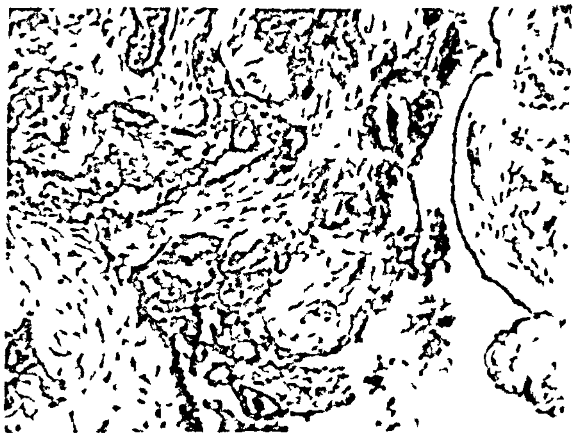

Fig 4—Case 4 Small cuboidal and flat celled tubular secondary carcinoma in omentum Ovary is probable primary site but peritoneal endothelioma is a possibility (×114)

Case 4.—Admitted in October, 1952, with a three-month history of abdominal swelling, weakness, and weight loss She was ill and wasted The fingers were clubbed Coarse crepitations were heard at bases of both lungs Chest X-ray showed diffuse reticulation in both lower zones with bilateral pleural thickening The sputum contained asbestos bodies There was ascites, and a mass was felt on vaginal examination At laparotomy, a mass of growth filled the pelvis, and there were nodules in the omentum and over the anterior abdominal wall A biopsy was taken, and histological examination showed a secondary carcinoma composed of small, cuboidal, tubular, and flat cells in omentum (fig 4) The ovary was thought to be a probable primary site, though a peritoneal endothelioma could not be excluded. She was admitted on two further occasions for paracentesis, but died at home and necropsy was not performed

Case 5 —Admitted in February, 1953, at the age of 52, with a six-week history of bearing-down pains in the lower abdomen radiating to the vagina and thighs The pain was worse on defæcation and micturition, but there had been no change in bowel habits and no blood in stools or urine She worked in the mattress department of an asbestos company for three years from the age of 16, and had been breathless on exertion for some years but denied having had a cough She was ill and wasted. The fingers were not clubbed There were bilateral basal crepitations, and X-ray examination showed pleural thickening at the right base, and fine reticulation throughout the lung-fields The sputum contained asbestos bodies, but no tubercle bacilli or neoplastic cells The liver was enlarged, hard, and irregular, and pelvic examination revealed a craggy mass in the pouch of Douglas The stools contained no occult blood and a catheter specimen of urine was normal. She was thought to have peritoneal carcinomatosis and further investigations were unjustifiable She died at home some weeks later, and no postmortem examination was made

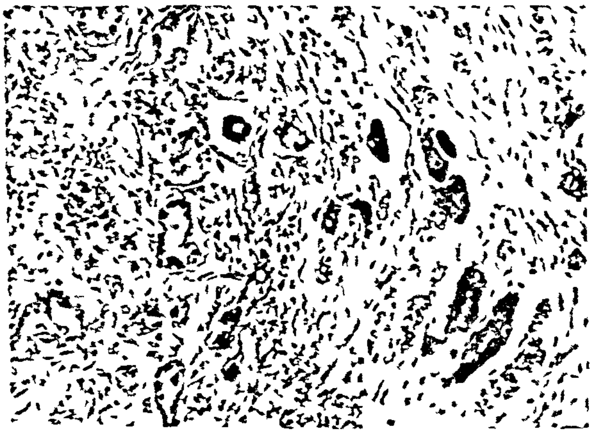

Fig 5—Case 6 Tubular and occasionally papillary, cuboidal-cell carcinoma suggestive of ovarian origin. (×114)

Case 6 —Admitted at the age of 54, when she gave a history of exertional dyspnœa for several years, severe unproductive cough for seven months and pleurisy four months earlier Her main symptom was lower abdominal pain, associated with anorexia and weight-loss The chest was emphysematous but there were no added sounds, and the fingers were not clubbed Chest X-ray showed no definite abnormality, but the sputum contained numerous asbestos bodies There was suprapubic tenderness, and on pelvic examination the uterus was felt to be enlarged, irregular, and fixed At laparotomy, free fluid was present and the pelvis was filled by a mass of growth of undetermined origin There were nodules of growth throughout the peritoneum A biopsy specimen was taken and histological examination showed a carcinoma made up of papillary, tubular, and cuboidal cells, suggestive of an ovarian primary (fig 5) She died four months later and postmortem examination was not made.

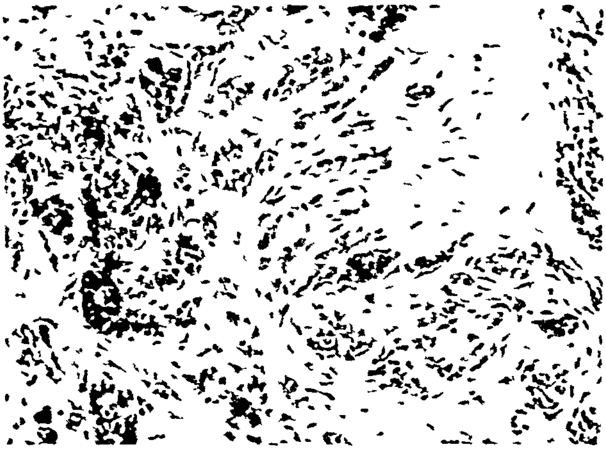

Fig 6—Case 7 Nodule of secondary carcinoma from peritoneum, composed of solid trabeculæ of polygonal cells (×120)

Case 7 —Thought to have asbestosis when she was admitted at the age of 38, complaining of abdominal swelling for six weeks She was obese and dyspnœic with impaired percussion note at both bases and bilateral basal crepitations Chest X-ray showed diffuse mottling throughout both lungs with pleural thickening at the left base No asbestos bodies were found in the one specimen of sputum examined Free fluid was present in the abdomen, and a mobile mass was felt in the hypogastrium At laparotomy, the omentum and peritoneum were studded with miliary nodules The ovaries were cystic and studded with growth, but were not apparently the primary site The histological appearance was that of secondary carcinoma in omentum, composed of solid trabeculæ of polygonal cells (fig 6) She died at home six months later, and no postmortem examination was made

Case 8 —Admitted at the age of 59 She had worked in the slab-making department of an asbestos factory for one year when she was 21 There had been no subsequent chest symptoms and the chest X-ray showed no abnormality, but her sputum contained numerous asbestos bodies She complained of malaise for one year and of increasing girth for five months There was gross ascites, with an irregular mass in the left hypochondrium and another in the pelvis A barium enema showed some narrowing in the region of the splenic flexure, thought to be due to extrinsic pressure, but no intrinsic lesion of the colon At laparotomy, the mass in the upper abdomen was found to be rolled up omentum, invaded by growth, and there were nodules of growth throughout the peritoneum The ovaries were atrophic and also studded with growth No abnormality was found in the stomach or intestine The appendix and a piece of omentum were removed for histological examination, which

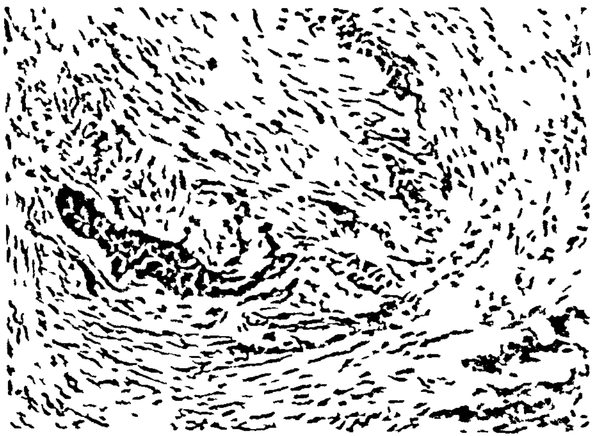

Fig 7—Case 8 Dense subserous fibrosis and lymphocytic infiltration with ill-defined tubules of polygonal and cuboidal cells that show no cytological evidence of malignancy (×144)

showed very dense subserous fibrosis and lymphocytic infiltration, with ill-defined tubular inclusions lined by polygonal cells that showed no cytological evidence of malignancy (fig. 7). The patient was seen once more in outpatients two months later, when the abdomen was said to be solid with growth. She died at home shortly afterwards and necropsy was not performed.

Case 9.—A 35-year-old woman was admitted to a gynæcological ward with a three-month history of gradual enlargement of the abdomen. No history of exposure to asbestos was recorded in the notes, but her sister was noted to have died from lung cancer secondary to asbestosis. There was dullness to percussion at both lung bases, with diminished breath sounds and coarse crepitations. The abdomen was greatly distended with fluid. Chest X-rays showed loss of translucency over both sides of the diaphragm, and the sputum contained asbestos bodies. At laparotomy, hard nodular swellings were found along the mesenteric border of the small intestine and studded over the omentum. The ovaries, liver, kidneys, appendix, and uterus were normal. The patient died seven weeks after operation.

Necropsy.—A layer of soft white growth covered the visceral peritoneum over the intestines, stomach, and pelvic viscera. There was similar growth over the under surface of the left lobe of the diaphragm and over the posterior adbominal wall. The ovaries were normal, but their surfaces were covered with growth. In the chest, there were tough fibrous adhesions between the right dome of the diaphragm and the lung, and two plaques of hyaline fibrosis in the pleura over the left dome of the diaphragm. No growth was found in the hilar lymph-nodes. There was diffuse fibrosis throughout the lower lobes of both lungs, with areas of confluent slaty-black anthracosis. No primary growth was found anywhere. Histological examination showed a neoplasm composed of solid, large polygonal cells with some papillary-cell and small-cell areas, associated with cleft formation. Occasional areas showed a transitional-cell pattern (fig. 8).

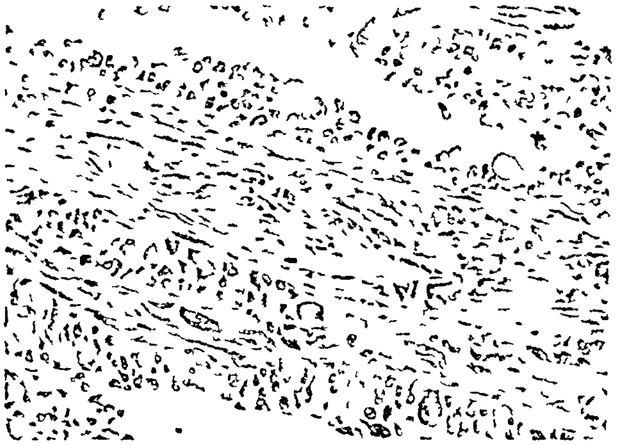

Fig. 8.—Case 9. Mainly solid large polygonal cell neoplasm with some papillary and some small-cell areas with cleft formation. A few areas show a transitional pattern. (×110.)

Case 24.—Admitted at the age of 50. Three years earlier, a diagnosis of asbestosis had been made. One year before admission, he attended outpatients with an eight-month history of epigastric discomfort, unrelated to meals but worse at night. There were no abnormal signs and a barium-meal examination showed no abnormality. He had some relief from alkalis, but vague abdominal discomfort persisted, and for two months before admission there had been loss of appetite with increasing girth. He was ill and wasted. The percussion note was impaired at both lung bases and there were bilateral basal crepitations. The abdomen was tense with fluid, but, after paracentesis, a large epigastric mass was felt. Chest X-rays showed diffuse reticulation, maximal in the lower zones. The sputum contained asbestos bodies. He died after three months in hospital.

Necropsy.—Firm fibrous thickening of the parietal pleura was present over the posterior chest wall, particularly on the right. There was slight diffuse fibrosis of the visceral pleura throughout, with underlying anthracotic flecking. The lungs showed slight diffuse induration, with scattered areas of anthracosis. No macroscopic carcinoma was found in the bronchi, or hilar lymph-nodes. In the mesentery of the ileum, a nodular firm fibrous mass was found which separated easily from the posterior abdominal wall. There were numerous nodules of growth in the lesser omentum, and around the pylorus of an otherwise normal stomach. Further nodules and plaques of growth were found throughout the peritoneum, in many places indenting the mucosa of the large and small bowel, but nowhere infiltrating the mucosa. On histological examination, the tumour shown was composed of small cuboidal cells with papillary, cleft-like, and tubular formation. There were a few areas of larger, less well-differentiated cells, and also some areas of myxomatous degeneration. This neoplasm was present in the serosa of ileum, spleen, and the peritoneal surface of the diaphragm, with one solid trabecula of cells extending through the diaphragm into the hyaline, fibrotic pleural surface. There were small clumps of cells in a carinal lymph-node, which also contained asbestos bodies. In the lungs, there was moderate peribronchiolar and pleural fibrosis with numerous asbestos bodies. A little bronchiolar epithelial hyperplasia was seen in the right lower lobe.

Discussion

Asbestosis

The first recorded case of pulmonary asbestosis was that of a patient who died in Charing Cross Hospital, London, in 1900. Details were given to the Departmental Committee on Compensation for Industrial Diseases (1907), by Dr. Montague Murray. It was not until 1930, when a further inquiry was held (Merewether 1930a and b, Merewether and Price 1930), that asbestosis was recognised as an industrial disease in this country and measures were taken to prevent it. By the nature of the work involved, these measures were unlikely to be wholly successful, and it is of interest that of the 42 cases in this series, ten (8 men and 2 women) were first exposed after 1930.

Asbestosis and Lung Cancer

Lynch and Smith (1935) reported the first case of lung cancer associated with asbestosis. In 1952, Hueper (1952) was able to collect 61 published examples. Of 99 detailed by Hueper (1955), 82 originated in England. The first statistical review was that of Merewether (1947), who reported the finding of lung cancer in 13.2% of 235 necropsies on patients with asbestosis. This was compared with an incidence of 1.32% among 6884 cases of silicosis. Wyers (1950) reported an incidence of 14.8% among 115 necropsies, and Gloyne (1951) found lung cancer in 14.1% of deaths associated with asbestosis. Doll (1955) provided further confirmation of a causal relationship with his investigation of necropsy reports on 105 persons who had been employed at one asbestos works. Lung cancer was found in 15 of 75 cases with asbestosis, and in 3 of the 30 cases without asbestosis. He concluded that the risk of lung cancer among men employed for twenty years or more was ten times that of the general population.

Such a direct association is not universally accepted. Jacob and Bohlig (1955), in Dresden, studied 343 cases of asbestosis and found only 4 cases of lung cancer, but 15 of associated active tuberculosis. They state that, during the past twenty years, the average number of asbestos workers throughout Germany has varied between 3000 and 4000 but that only 17 cases of lung cancer have been reported among them. Braun and Truan (1958) criticise statistics based on necropsy findings without reference to the population at risk. In an epidemiological study of over 6000 workers in the asbestos mines of Quebec, they found only 9 proved lung cancers—an incidence of 25·3 per 100,000 of the population studied. Comparing this incidence with that of 22·5 per 100,000 for the rest of the province of Quebec, they conclude that the absestos workers do not have a significantly higher death-rate from lung cancer than do comparable sections of the general population.

The present series is too small for statistical analysis, but it will be seen that the incidence of lung cancer at necropsy is very much higher than any previously reported—particularly among the men, where it is 67%. This is largely explained by selection, since 6 of the 10 men were referred directly to the medical and surgical thoracic units from other hospitals with the diagnosis, either provisional or established, of lung cancer. The same explanation does not hold for the females, who all attended at general medical outpatients, thus giving a lung cancer incidence of 26% of all deaths associated with asbestosis. It will be seen from table III that the average duration of exposure of the 4 women with lung cancer was only about nine and three-quarters years whereas the average period from first exposure to death was twenty-five years, suggesting that time of exposure is not the most important factor in the development of lung cancer. Merewether (1947) also noted that the average age of death with asbestosis and carcinoma of lung was about fifty-two years against about forty-four years for those with asbestosis alone, though there was little difference in the duration of exposure. Hueper (1951) draws the conclusion that many of these patients die from asbestosis before their lung cancers have time to develop.

TABLE III—PERIOD SINCE FIRST EXPOSURE AND DURATION OF EXPOSURE OF 35 CASES OF ASBESTOSIS, ASBESTOSIS WITH LUNG CANCER, AND ASBESTOSIS WITH PERITONEAL CANCER

—	Number of cases		Years since first exposure		Duration of exposure (years)	
	M	F	M	F	M	F
Asbestosis and peritoneal cancer	1	8	26	30·7* 21–38†	23	5·8* 1–21†
Asbestosis and lung cancer	10	4	24·6* 5–45†	25* 15–38†	14·3* 2–45†	9·7* $^{1}/_{12}$–20†
Asbestosis alone (living)	4	9	30·0* 18–42†	23·5* 18–33†	19·1* $^{1}/_{2}$–42†	7·2* 3–17†

* Average. † Range.

As in other reported series, there is no great preponderance of any one cell type. Of 15 lung cancers, 5 were squamous, 8 anaplastic, and in 2 others the type was not stated. It is worth noting that the 4 women with lung cancer were all nonsmokers.

Asbestosis and Peritoneal Cancer

Leicher (1954) reported the case of a 53-year-old asbestos worker who had suffered from asbestosis complicated by pulmonary tuberculosis for several years, and who died in 1952 from tuberculous meningitis. At necropsy, the peritoneum was found to be studded with nodules of growth and there were plaques of growth over the peritoneal aspect of the diaphragm. This was thought to be a " primary cortical cell tumour of the peritoneum." No typical asbestos bodies or fibres were seen in the tissues of the tumour, but asbestos was demonstrated there by X-ray-diffraction techniques. Bonser et al. (1955) appear to have made the only previous reference to a high incidence of abdominal neoplasms associated with asbestosis. Out of their series of 72 cases, 4 (1 man and 3 women) had peritoneal cancers. Of the 3 women, 2 had been thought to have ovarian primaries (Bonser 1959).

TABLE IV—CAUSES OF DEATH OF 15 MEN AND 15 WOMEN WITH ASBESTOSIS

—	Men	Women
Ovarian or peritoneal cancer	1	9 (60%)
Carcinoma of lung	10 (67%)	4 (26%)
Pneumonia	2	
Other causes	2	2

In the present series, 9 of 15 deaths in women were associated with ovarian or peritoneal cancer, an incidence of 60%. In one case (no. 5) the diagnosis was only clinical, and there was nothing in the history or examination to incriminate any particular organ as the site of the primary lesion. In the remaining 8 cases, either laparotomy or postmortem examination was performed. Only 1 (case 1) had a definite ovarian neoplasm without peritoneal involvement. In every other case there was diffuse peritoneal growth with ascites. In 4, the pelvis contained a mass of growth and the ovaries were not identified. In 2 other cases, the ovaries were said to be studded with growth but were not, apparently, the site of the primary lesion; in 1 case the ovaries were cystic but not involved by growth.

Case 24 was the only man to show a similar picture of diffuse peritoneal cancer. An intensive examination revealed no macroscopic evidence of a primary growth, but subsequent microscopy showed bronchial epithelial hyperplasia in the right lower lobe, and tumour-cells in a hilar lymph-node. In addition, there was a solid trabecula of growth extending through the diaphragm, which may have arisen on either the pleural or the peritoneal aspects. In this case, and in case 9 where plaques of growth were also found on both aspects of the diaphragm, the possibility of a missed bronchial primary is more difficult to refute.

It is possible that these cases do not represent a new pathological entity but are all cases of secondary carcinoma from bronchial primaries. The occurrence of secondary deposits from bronchial carcinoma, many months before there is clinical or radiological evidence of the primary lesion, is familiar to all. Even at necropsy, a small primary growth in the wall of a peripheral bronchus is easily missed unless specifically sought. The absence of clinical or radiological evidence of lung cancer in the 10 cases of peritoneal cancer described does not eliminate this possibility, nor will the negative record of such a primary entirely convince the sceptical. Yet the findings differ from those usually associated with carcinomatosis from lung cancer in which it is common to find deposits in liver, adrenals, and kidneys, but most unusual to see diffuse peritoneal involvement without such deposits. However, Bonser et al. (1955) and Bonser (1959) attach importance to the plaques of hyaloserositis tethering the base of the lung to the upper surface of the diaphragm in many cases of asbestosis, as in case 9 and case 24 of this series. They consider that the consequent alteration of lymphatic drainage of the region offers a means of spread to the abdomen of cancer arising in sequestrated bronchial epithelium. On the other hand, this explanation is difficult to relate to the predominance of women in the present series, since lung cancer is commoner among the men.

2 of Bonser's 3 patients with asbestosis and peritoneal cancer were thought to have primary ovarian growths. Case 1 of this series was undoubtedly ovarian, and, in 4 others, the ovaries were involved in a mass of growth filling the pelvis and may well have been the site of the primary lesion. In all cases, the histological findings have been compatible with ovarian carcinoma and this has been

the diagnosis in most cases In spite of this, and of the fact that all but one of the cases in this series have been women, some doubt must be cast on this diagnosis In 3 cases in which the ovaries were identified they appeared not to be the primary site, and, though ovarian carcinoma is the commonest cause of undifferentiated peritoneal cancer in women, it is possible that these organs have become a dumping-ground for other cases of "carcinomatosis *peritonei*" in which no definite primary can be demonstrated

Wyss (1953) reported the findings of asbestos fibres in the urine of patients with asbestosis Stovin (1959) found asbestos bodies in the thyroid of case 38, at necropsy, and Bonser (1959) states that asbestos fibres were found in the spleen of one of Stewart's cases of asbestosis These were chance findings and it is possible that more diligent search, such as that of Leicher (1954), might produce further evidence of a hæmatogenous spread of asbestos fibres and their eventual deposition in extrapulmonary tissues It is beyond the scope of this article to review the evidence for "chemical" versus "mechanical" carcinogenesis in asbestosis, but there is much support for the former concept If this be accepted, it is conceivable that peripherally deposited asbestos may provoke local neoplastic change McLaughlin (1959) has described a carcinoma on a doctor's finger at the site of penetration by asbestos fibres

It remains to be explained why the peritoneum should be so frequently involved without any reported increase in other extrapulmonary neoplasms Primary mesothelial tumours are rare, and even the concept of "pleural mesothelioma" has now been largely abandoned in favour of lymphatic spread from an underlying bronchial neoplasm or primary growth elsewhere (Smart and Hinson 1957, Hinson 1958) Hugh-Jones (1960), however, suggests that this type of tumour is more common in patients with asbestosis Vorwald et al (1951) suggested a mechanical factor, related to length of fibre, in the production of asbestosis, and in the course of their experiments on rats were able, by injecting asbestos fibres, to produce a fibrotic reaction in the peritoneum, but not in liver, spleen, or subcutaneous tissues They attributed this to movement taking place between peritoneal surfaces It has been suggested that such fibrosis may play a part in the development of neoplastic changes, and this is supported by the recent work of Menkin (1960), who produced evidence of a growth-promoting factor in inflammatory exudates and suggested that this may act as a cocarcinogen Such a factor, together with the "chemical" factor in asbestos, may determine selection of the peritoneum as the site of tumour-formation following the transdiaphragmatic or hæmatogenous spread of asbestos fibres To support this theory it would be necessary to demonstrate the earlier stage of peritoneal inflammation in patients with uncomplicated asbestosis The further difficulty of the great predominance of women with peritoneal cancer in this series might be explained by the greater disposition of men to lung cancer, whether this be related to sex, associated bronchitis, smoking habits, or air pollution It will be seen that the average period after first exposure for the 14 patients with lung cancer was under twenty-five years compared with thirty years for the group with peritoneal cancer

It is clear that no single satisfactory explanation for these cases can be drawn from the available material, though they appear to form a clinical entity of statistical significance

2 cases in this series require further comment In case 8 there was a clear history of exposure to asbestos dust, and her sputum contained asbestos bodies thirty-three years after exposure ceased In spite of this, she had no chest symptoms, X-rays of her chest showed no definite abnormality, and she could not be said to have asbestosis From the clinical course and operative findings there can be little doubt that she had peritoneal cancer In a similar way case 27 developed lung cancer with asbestos bodies in his sputum twenty years after removal from exposure to asbestos dust, without any intervening symptoms or radiological changes to establish a diagnosis of asbestosis Clearly the question of chemical carcinogenesis, whether it be due to the asbestos itself or to some product of its reaction with the tissues, is of medicolegal interest in these cases In the past, Hueper (1951) has commented on "the apparent dependence of cancerous changes in the lungs of asbestos workers upon the presence of asbestosis"

Summary

23 female and 19 male cases of asbestosis are summarised with details of type and duration of exposure, period since first exposure, and associated disease

Of 30 deaths (15 men, 15 women), there were 14 who died with lung cancer—10 in men and 4 in women This high incidence among the men is partly explained by selection, but this does not apply to the women, who were all non-smokers

9 women and 1 man died with ovarian or peritoneal cancer This appears to be more than a chance association, and spread from undiagnosed lung cancer seems unlikely At least four of the tumours were not of ovarian origin Some evidence of hæmatogenous spread of asbestos fibres is adduced, and it is suggested that a combination of mechanical and chemical factors may determine the peritoneum as the site of inflammatory and subsequent neoplastic change

Attention is drawn to the occurrence of bronchial carcinoma in one patient and of peritoneal cancer in a second The sputum of both patients contained asbestos bodies many years after removal from exposure, but there was no other evidence of asbestosis

I am indebted to Dr K M A Perry, Dr A I G McLaughlin, Prof D S Russell, and Dr G M Bonser for much advice and criticism in the preparation of this article Dr P G Stovin of the Bernhard Baron Institute of Pathology at the London Hospital kindly provided the photomicrographs, and was responsible for many of the pathology reports

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THE PROBLEM OF PULMONARY EMPHYSEMA

THE MISSING LINK BETWEEN STRUCTURE AND FUNCTION

ISRAEL RAPPAPORT
M.D Columbia, N Y

EDGAR MAYER
M.D New York University

NEW YORK

PULMONARY emphysema has remained an enigma because of the failure to find the natural link between structure and function in the lungs This has now been realised, and more information is being sought on the form and function of pulmonary structures Long ago, we proposed a new concept of the relationship, on the basis of which emphysema can be interpreted as pulmonary insufficiency

Since then, much new evidence has appeared that the terminal structures of the lungs in vivo have activities such as we postulated—activities which have previously remained unnoticed in studies of dead organs Although our views are still largely hypothetical, there are sufficient data for a new approach to the problem of emphysema

Past and Present Hypotheses

Laennec was obviously aware of the need to explain pulmonary emphysema by a link between structure and function He named the disease for the distended airspaces which he believed to be its essence Considering the state of knowledge in his time, it was natural for Laennec to believe that the visible movement in breathing is the sole function of the lungs He believed that emphysema was most reasonably explained as the mechanical effect of obstructed breathing

Laennec conceived of a special type of inflammation causing obstruction in the bronchioles Villemin logically speculated about a special affection of the myoelastic structures concerned with the failing elastic recoil of the lungs The majority of pathologists and clinicians since Laennec have continued to discuss various morbid changes of acquired or inherited origin in the different component structures (vessels, bronchi, connective tissue fibres) which lead to their weakening by destruction or atrophy, and so lay the lungs open to mechanical distortion of its architecture by forces of breathing Since the major force in breathing is exerted by the bellows mechanism of the thorax, it was only natural that many observers looked upon changes in the thoracic bone structures as the primary cause of emphysema.

In modern times, the trend has been to return to Laennec's idea of bronchial involvement as the primary cause

Some observers speak of an active function of the bronchi disturbed by a variety of agents—infection (McLean 1958), allergy (Lister 1958), or toxic damage by air pollutants (Heppleston 1954) Bronchial dysfunction is assumed to be the factor in overdistension of air spaces by air trapping due to collapse of bronchioles, collateral ventilation, and the mechanical effects of disturbed breathing Some observers (Dayman 1956) object to the assumption that active bronchial function is superfluous since the mechanical effects of disturbed breathing—air trapping and its sequelæ—are well explained even without active function of the bronchi

In these pathogenetic concepts, the only common denominator is the lung conceived as primarily an organ of motion, the mechanics of which are such that, when they are disturbed, distortion of its architecture results This takes the form of emphysematous distension of the air spaces It has long been recognised that practically all affections of the lungs can cause this The multiplicity of potential origins became so bewildering by the turn of the century that Hoffman (1904) stated that emphysema, as a primary idiopathic disease of uniform ætiology, was a mere myth Now, half a century later, Liebow (1959) again points to the futility of seeking for a single cause Yet the myth of primary emphysema continues to survive Chronic bronchiolitis and bronchitis of insidious origins and subclinical progress are supposed to initiate the mechanical pathogenesis described

All this time, pulmonary physiology has been concerned with measurement of ventilatory turnover of air, and of breathing capacity, with measurement of the forces involved in breathing, with compliance of the structures of the lungs and chest, and with measurements of resistance to air flow in the airways These parameters of breathing and ventilation are usually equated with lung function proper, particularly in reference to emphysema Pulmonary physiology can be said to have grown out of the study of emphysematous patients In them, disturbed ventilation is an early manifestation which lends itself to exact measurement This favoured the equation of ventilatory activity with pulmonary function, and tended to confirm the mechanical concept Thus modern physiology has promoted the survival of Laennec's ideas, and perpetuated the belief of the lungs as an organ of motion These beliefs are responsible for the failure to solve the problem

It is remarkable that such concepts of Laennec have survived in spite of a century and a half of increasing knowledge of pulmonary medicine

Adherence to the mechanical concept of lung function and of emphysema has mainly been responsible for failure to relate this disease to the primary function of the lungs —namely, gas exchange Modern physiology has not neglected the study and measurement of pulmonary gas exchange Ingenious gas analytical techniques have been elaborated, and are used to measure gas diffusion-rates and pressures Abnormalities in gas exchange are now attributed to impaired ventilation and circulation, and are interpreted mostly in terms of impaired distribution of these through all parts of the lungs

The prevailing teaching is that gas diffusion in the lungs is determined solely by the efficiency of ventilation and by the blood-flow in the alveolar capillaries The ultimate factor in controlling the surface available for gas diffusion is presumed to be the efficiency of the cardiocirculatory pump Since gas diffusion is a purely physicochemical process, the structures of the surface over which diffusion takes place are denied any active role in this function The structures of the vast diffusion surface are assumed to serve only as a medium through which the gases pass, as through any other inert medium The possibility that these structures could play an active role in the regulation of the diffusion surface has been overlooked, in spite of increasing evidence of frequent diffusion differences which cannot be explained by altered ventilation or circulation In a large group of pulmonary diseases, gas diffusion is impaired, even though ventilation and circulation are increased For these, the term " alveolar block due to organic tissue changes " has been conceived as an explanation to emphasise the wholly passive role of the diffusion surface Recent studies, however, have revealed many instances of reduced diffusing capacity without such changes in the alveolar structures, and with normal ventilation and circulation Indeed, this has been a most common finding in so-called non-obstructive emphysema (Rappaport and Mayer 1954).

Loss of diffusion surface in later life—and often, too, in the relatively young is an unexplained finding. Frequent discrepancies between efficiency of breathing and diffusing capacity have greatly increased the breach in the concept of the lung as an organ of motion. This hypothesis no longer suffices to explain abnormalities in lung function. If we consider that the ultimate function of the lungs is concerned with diffusion of gases across the surface membrane, the structures of which are not involved in the movements associated with pulmonary ventilation and circulation, we are forced to conclude that the concept of the lung as an organ of motion has never been based on a natural link between structure and function. To find that link we must conceive an active role of the structures of the surface membrane in the maintenance of extent and quality of the diffusion surface.

Structure and Function of the Diffusion Surface

It has often been said that the bodily organs are miracles of biological engineering in that structures are adapted to their specific functions. This biological process is seen at its best in the lungs, the structures of which are wonderfully adapted to their primary function which is to create surface for diffusion of gases. Gas diffusion calls for a surface of extraordinarily large extent and yet of extreme delicacy—i.e., the largest possible surface of exposure with the least possible amount of tissue interposed between air in air spaces and blood in capillaries. The lungs consist of a vast number of airsacs, endowed with the capacity to create an internal surface the size of about half a tennis-court—a surface of such exquisite delicacy that its thinness is said to be unequalled in the body, a surface constantly recreated in form of a semifluid film, even while the frame structures of airsacs, bronchioles, and vessels retain the high degree of mobility required for ventilation and circulation.

Although the bulk of the lungs consists of air, they appear to the eye as solid organs because the air is contained in a vast number of tiny airsacs. These are generally thought of as small balloons, alternately inflated and deflated by the bellows mechanism of breathing. There is evidence, however, that these tiny airsacs take but little part in expansion and retraction of the lungs, and that the large volume changes occur in centres of airsacs in the millions of ducts and bronchioles (Hartroft 1945). Most of the lung volume is ventilated by molecular diffusion, which presumably begins at the bronchiolosaccular junctions (Roos et al. 1955).

The arrangement of the lung appears to be that of a vast honeycomb. Crowding of a prodigious number of airsacs into a small space is accomplished by infinite dividing and subdividing. Enormous increase of internal surface is accomplished by partitioning—i.e., alveolisation within airsacs. Creation of diffusion surface in airsacs goes even beyond this. The alveoli have an exceedingly rich network of capillaries of very fine mesh. These capillaries are endowed with "erectile activity" and, when filled with blood, bulge forward into the airspace (Rappaport and Muller 1938, Jaykka 1957). This is made possible by the special nature and activity of the alveolar lining membrane, which consists of an exceedingly delicate diaphanous jelly-like film of changeable quantity and consistence. The substance for this membrane, secreted by special types of cells placed at the junctions of airsacs and bronchioles, has the unique power of reducing the surface tension to near zero (Bremer 1938, Macklin 1954, Pattle 1958). Surface tension over the curved surface of the tiny airsacs would otherwise be so high that they would contract, and would require many times greater force of thoracic traction to keep them patent.

Creation and maintenance of diffusion surface by activities of terminal lung structures was postulated by one of us (I. R.) many years ago, and was recently described again as "visceral lung function" (Rappaport 1954). Much evidence in recent experimental and pathological work supports this view (Radford 1959, Clements 1958, Hayek 1956).* So far, only a beginning has been made in discovering the function of the ultimate structures, but we already have one testing method which affords at least an approximation of this function. On the assumption that "visceral function" operates in diffusing-surface creation and maintenance, it may be inferred that diffusing-capacity determinations may afford an approximate estimate of extent of this surface. As already indicated diffusing-capacity changes are quite independent of changes in ventilation. Breathing capacity is often high when diffusing capacity is low, and vice versa. These tests obviously measure different categories of function rather than different phases of lung function. When more is known about the nature of this, it is conceivable that chemical assay of enzyme-activating or hormone-activating cells that secrete the substance for the constantly flowing membrane of diffusion surface may afford a more precise estimate of "visceral lung function".

We may conclude, therefore, that ventilation serving to refresh air in the lungs is an auxiliary function. Diffusion-surface creation is the primary function of the lungs. The alveolocapillary interface is an extraordinary surface constituted by unique structures which are actively engaged in constant maintenance and adaptation of diffusion surface. "Visceral lung function" refers to activity of these structures in constant creation of diffusion surface, and in autonomic regulation of the quality and extent of this surface in accord with momentary requirements for gas exchange. There is ample evidence of autonomic function of the bronchiolosaccular structures, which may be reasonably interpreted as serving the constantly changing living diffusion surface. The lungs are provided with an enormous reserve of airsacs sufficient for the needs of severe exertions in which function must be greatly increased. We postulated that during basal conditions of resting function, only a minimal extent of surface-creating activity continues in some only of the airsacs, not all of which function at one time.

Homœostatic correlation of the function of pulmonary, cardiac, and chest bellows with ventilation and circulation in the lungs has long been established. One of us (I. R.) postulated also the existence of homœostatic regional correlation of ventilation and perfusion throughout all parts of the lungs as indispensable to its visceral function. The fact of autonomic control of regional function has been confirmed in recent physiologic studies (Euler 1957). This supports our assumption that airsacs in which visceral function has ceased for any reason are also shunted from ventilation and circulation. This applies to alternation of function in the airsacs from rest to exercise under normal conditions, as well as under pathologic conditions.

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* Lack of space permits only a sampling of references to recent work on activities of the alveolar surface membrane structures. The literature on this is already extensive and has been rapidly increasing.

in which whole lung areas are eliminated from function which must be taken over by the intact parts of the lungs.

The problem in emphysema now becomes one of working out its evolution from “ visceral dysfunction ” in an increasing number of airsacs to “ pulmonary insufficiency ” in the whole of the lungs.

The Evolution of Pulmonary Emphysema

Emphysema evolves from “ airsac emphysema ” to emphysema involving the lungs as a whole, and so becomes a manifestation of pulmonary insufficiency in the strict sense of this term.

The basic lesion in “ airsac emphysema ” is the damaged airsac which ceased to function in diffusion-surface creation leaving only shallow vestiges of alveolar septi. This change is functional, implying failure of “ visceral function ”—i.e., creation of diffusion surface as outlined above. Non-functioning air spaces, enlarged by coalescence of alveoli and kept open by thoracic traction, become subject to mechanical enlargement by air trapping and collateral ventilation due to two factors: (1) the effect of thoracic traction up to a certain point is the greater the larger the air space (Head 1951), and (2) enlargement of airspaces leads to relative airway obstruction. The lumina of fine bronchioles are not widened apace with enlarging air spaces, and, the larger the air space, the relatively narrower its inlet bronchiole becomes. Thus, air space enlargement and airway obstruction are both natural consequences of “ airsac emphysema ”. Failure of visceral function in individual or in groups of airsacs, with its consequences of mechanical enlargement, result in *anatomical emphysema*. This may involve many airsacs in certain parts, or may be widespread over the lungs.

Failure of visceral function in individual airsacs or in groups of them may result from any damage to their delicate structures. This includes the whole gamut of infections—allergic inflammations, and toxic (physical or chemical) agents which reach these structures either by the blood-stream or by inhalation (fine aerosols). It is clinically established that, in acute damage, the visible pulmonary infiltrations may completely resolve, yet leave the delicate structures permanently injured so that emphysema may appear abruptly (Rappaport 1955). Chronic inflammatory processes and long-continued toxic damage are more apt to result in fibrotic obliteration of lung tissue. If these are extensive, and pulmonary reserve becomes exhausted, they lead to emphysema in the unaffected part of the lung by way of compensatory hyperfunction.

Failure of visceral function may also result from long-continued and excessive compensatory hyperfunction in lung areas in which available reserves of functioning airsacs have become inadequate. This is often seen to develop after resections of whole lungs, or large parts of both lungs, when the remainder lacks adequate reserves for compensatory function. In principle, this in no way differs from emphysema which develops in remaining unaffected parts of the lungs in the great variety of diseases which render functionless increasingly large proportions of available reserves of airsacs. The term “ compensatory emphysema ” has previously been applied to the overexpansion of unaffected parts of the lung which were engaged in truly compensatory function. At the present time, the term “ compensatory emphysema ” is applied to describe the failure of compensation in areas unaffected by the primary pulmonary disease or remaining after resection of large parts of the lung. There is reason to believe that interference with ventilation and circulation is here a factor in eventual failure of visceral function in airsacs long burdened by excessive compensatory hyperfunction. We have observed development of emphysema in lung areas where circulation has changed from venous to systemic arterial blood-flow by way of collaterals from bronchial or pleural arteries. Essentially the same principle is involved in so-called “ unilateral emphysema ” which develops on the basis of hypoplasia of a branch of the pulmonary artery (Belcher et al. 1959).

Finally, we have postulated that pulmonary emphysema may also develop on basis of “ lung defects ” of postnatal developmental origin (Mayer and Rappaport 1953). From our clinical observations, we are convinced that there are cases in which the condition cannot be traced to pre-existing disease of any type and that some are particularly disposed to develop emphysema early in life as a result of trivial exposures, which do not so affect the vast majority of people similarly, or more severely, exposed. This disposition is due to pre-existing defects in the lungs of postnatal developmental origin.

To understand the evolution of chronic pulmonary emphysema, we must constantly bear in mind that the lungs consist of a vast number of airsac units which can all function together when necessary, but can also function separately and compensate one another in function. In every chronic pulmonary disease, regardless of origin, the affected lung units will be temporarily or permanently out of function, and this will be compensated by the function of remaining unaffected units. Emphysema is no exception to this, and, throughout its evolution, consists of combination of non-functioning overdistended units (irreversible anatomical emphysema) and compensating units which may show evidence of reversible overexpansion according to temporary need of compensation.

Emphysema refers to the whole overdistended state of the lungs. This always includes the combination of overdistended non-functioning units (anatomical emphysema) and overexpanded compensating units in greatly variable proportions. The greater the proportion of non-functioning units (anatomical emphysema), the more need there is for compensation by functioning units involving their overexpansion which may or may not be reversible depending on the need. The more advanced the emphysema, the less reversible the overexpansion, but even then it represents the most complex mixture of non-functioning decompensated airsacs and hyper-functioning compensating airsacs. The degree of pulmonary insufficiency is determined by the ratio of one to the other.

Continued mechanical overdistention and coalescence of non-functioning airsacs plays an important role in aggravating the emphysematous state. The mechanical factors involved include (1) increased effect of thoracic traction on non-functioning airsacs enlarged by coalescence of alveoli, (2) progressive loss of elastic recoil, (3) collapse or compression of bronchioles, (4) complicating bronchial inflammatory processes aggravating airway obstruction, and (5) combinations of any of these. Progression of emphysema by these distending factors is quite irregular, depending on local influences determined by the primary pulmonary disease or on subsequent complicating local infections. Mechanical overdistension is thus inseparable from the emphysematous state, and greatly aggravates it by increasing encroachment upon available space in the chest and upon functioning parts of the lungs. This mechanical part of the emphysematous state incidental to, though not inherent in, the process by which emphysema originates, contributes importantly to the progression of pulmonary insufficiency

Compensatory lung function implies that ventilation and perfusion are diverted from non-functioning to functioning airsacs The air contained in non-functioning airsacs must be obtained by diffusion or collateral ventilation by way of enlarging pores (Cohn) or by way of channels of Lambert (Lambert 1955) In the absence of normal perfusion from pulmonary arterioles, the blood circulation of non-functioning airsacs must be derived from systemic (bronchial) arterioles When large parts of the lungs have become non-functioning airsacs, the shift to systemic circulation is greatly increased and pressure in the pulmonary circulation as a whole rises in proportion Presumably this becomes the chief factor in development of cor pulmonale (Rappaport and Mayer 1957)

Summary

The problem in emphysema is, in final analysis, that of the function of the lung structures proper In lay terms the question is whether we are " winded " or " lunged " Past and current concepts have identified lung function with its activity in breathing Therefore emphysema became a matter of " shortness of breath " We conceive lung function to be a matter of the creation of diffusion surface by the activity of the structures of its innumerable airsacs, best described as " visceral function of the lungs " This implies that lung function is determined by the available supply of airsacs and the functioning efficiency of these in the maintenance of a diffusion surface adequate in extent and quality in accord with changing requirements of the body In lay terms this means that we are " lunged ", not just " winded " †

Emphysema is conceived as a manifestation of pulmonary insufficiency in the strict sense It implies inadequate diffusion surface for gas exchange either because of *insufficient number of airsacs* available for normal " visceral function ", or because of *inefficiency of their function* in maintaining adequate diffusion surface In the origin of pulmonary insufficiency these two possible causes are so closely linked that it is hardly ever possible to make sharp distinction between them It lies in the nature of visceral function that, as the proportion of functioning airsacs is reduced below a critical point, the function of remaining airsacs becomes increasingly inefficient with diminishing reserves

Emphysematous changes are inherent in the evolution of pulmonary insufficiency due to functional as well as to mechanical causes Clinically pulmonary insufficiency always consists of variable combinations of anatomical and clinical emphysema, in which a complexity of functional and mechanical factors, acting in a vicious cycle, continue to aggravate the emphysematous state by coalescence and overdistension of non-functioning, as well as by overinflation of compensating airsacs

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† After this article was submitted for publication we noted Dr Roger Bannister s paper presented to the Association of Physicians of Great Britain (Bannister, R G , Cotes, J E , Jones, R S , Meade, F [1960] *J Physiol* 152, 661) Dr Bannister has found that athletes have higher diffusion capacities, which affords them a higher rate of transfer of oxygen in the lungs He concludes that increased lung-diffusion capacity is more important than muscularity, exceptionally high cardiac output, or an extra large vital capacity This is indeed what we are implying in the above phrase, we are lunged , not just winded

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T-SUBSTANCE ANOMALY

AN INBORN ERROR OF PURINE METABOLISM

H M T Coles
M D Lond , M R C P , D C H
CONSULTANT PHYSICIAN, WESTMINSTER CHILDREN'S HOSPITAL, LONDON, S W 1

Ann Priestman
B M Oxon , D C H
REGISTRAR, WESTMINSTER CHILDREN'S HOSPITAL, LONDON, S W 1

J H Wilkinson
B Sc , Ph D Lond , F R I C
READER IN CHEMICAL PATHOLOGY IN THE UNIVERSITY OF LONDON, WESTMINSTER MEDICAL SCHOOL, LONDON, S W 1

THE child described here excretes a previously unknown substance in his urine This substance—provisionally named T-substance—has since been found in the urine of some of his relations Its exact nature is not finally determined, but it appears to bear a close chemical resemblance to alloxan It was discovered by urinary paper chromatography, done as part of an investigation of the cause of the child's physical and mental retardation, and is usually excreted in large amounts Subsequently it has been found in similar quantities in the urines of a five-year-old child, with delayed physical development but normal mentality, and in the urine of her brother who is normal Paper chromatograms of the urine of a mentally and physically backward infant of twenty months showed two similar spots This patient will be the subject of a later communication

Studies of the family of the first child are presented, and it will be seen that, inferentially, the abnormality of metabolism is transmitted as an autosomal recessive characteristic

A brief account of the chemical investigations in this case was presented at the Fourth International Congress on Clinical Chemistry (Wilkinson 1960)

The Patient

The child was born at full term on May 19, 1955, after a pregnancy complicated by anæmia The birth-weight was 6 lb 5 oz On the 1st day of life, he had a cyanotic attack, and was kept in an oxygen tent for 3 days When he was just over a month old, he had further cyanotic attacks, and was later sent to a cardiac unit for investigation A clinical diagnosis of Fallot's tetralogy was made, but, as he was obviously mentally

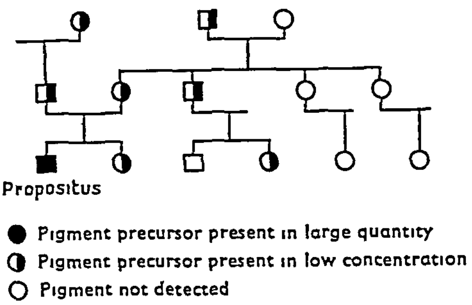
Propositus
● Pigment precursor present in large quantity
◐ Pigment precursor present in low concentration
○ Pigment not detected

Fig 1—Familial incidence of T-substance

defective, no further action was taken During 1956, he was several times admitted to hospital because of attacks of bronchopneumonia, heart-failure, and gastroenteritis

He first came under our care in April, 1959, when full investigations were undertaken to elucidate the cause of his lack of mental and physical development We found that his urine contained a hitherto unknown substance—probably a purine derivative Investigation of those members of his family from whom it has been possible to obtain urine, gave the results shown in fig 1

His mother says she had bilateral ptosis as a child, but this recovered spontaneously She now has established mitral stenosis One of his cousins, whom it has not been possible to test, is said to have bilateral ptosis The rest of the family are well

At 3 years 11 months, he was an active child with brown hair and brown eyes (fig 2A and B) There was bilateral ptosis associated with backward head-tilt, but the eyes themselves were normal He could stand alone, but could not walk unsupported His vocabulary was limited to two or three words

Measurements —Head circumference, 19^1/ in , crown–heel, 37 in , crown–pubis, 21 in , pubis–heel, 15^3/$_4$ in , ratio crown–pubis/pubis-heel, 1 27, span, 34 in , weight, 28 lb

Cardiovascular system —There was a soft systolic murmur, heard best down the left sternal border, but no cardiac enlargement or alteration in heart-sounds Femoral pulses were palpable, and the blood-pressure was 100/60 mm Hg No abnormality was discovered in the respiratory system or the abdomen, and muscle-tone was normal with normal tendon-reflexes and plantar responses

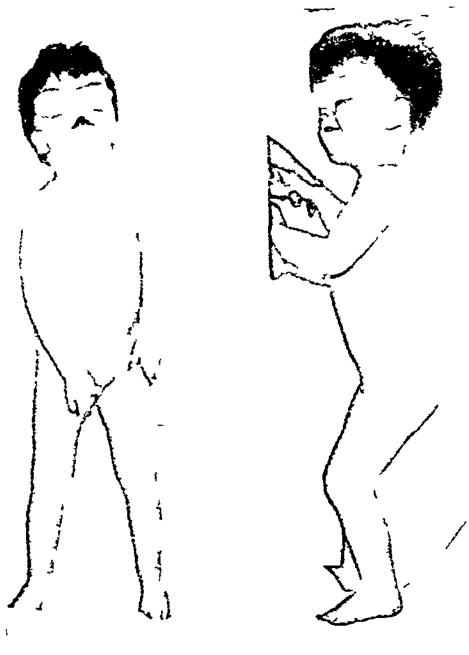

Fig 2A and B—The patient, aged 3 yr 11 mos

Investigations —Cardiac catheterisation and selective two-plane angiocardiography showed mild pulmonary hypertension, but no evidence of a shunt

Hæmoglobin 12 0 g per 100 ml , white blood-cells 10,000 per c mm (72% neutrophils, 25% lymphocytes, 3% eosinophils) Blood-urea 30 mg per 100 ml Serum-sodium 124 mEq per litre, serum-potassium 3 7 mEq , serum-chloride 86 mEq , serum-calcium 9 2 mg per 100 ml , serum-cholesterol 210 mg Serum-proteins and liver-function tests normal

Bone-age, chest and skull X-rays normal Urine faint trace of protein, but no pus cells or red blood-cells No reducing substances found

Urinary Aminoacids

The urinary aminoacids were investigated by paper chromatography of electrolytically desalted urine, according to the method of Bowden (1959) using quantities of urine containing 250 µg nitrogen on a Whatman no 1 paper

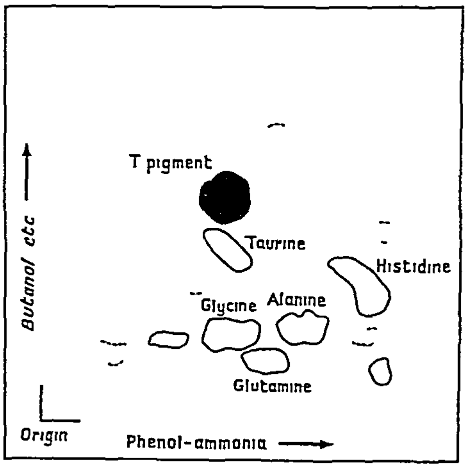

Fig 3—Tracing of a paper chromatogram from patient s urine, showing position of pigment in relation to principal aminoacids

Phenol-ammonia was used as the first solvent, and a mixture of butan-1-ol, butan-2-one, dicyclohexylamine, and water as the second The chromatograms were stained with ninhydrin to locate the aminoacids When he was first investigated, relatively large amounts of glycine, alanine, taurine, glutamine, and histidine were excreted, together with small quantities of serine and γ-aminobutyric acid There were traces of β-amino-*iso*butyric acid, threonine, valine, arginine, and aspartic acid Later specimens, however, showed normal patterns

During development in the first solvent system, a reddish-purple spot, having a mobility resembling that of taurine, appeared on the chromatograms It persisted during the run in the second solvent, in which it travelled somewhat faster than taurine (fig 3)

In over 200 urines examined by this method, this was the first time such a spot had been seen It persisted on a normal ward diet, free of sweets or other sources of dyes, and was not found in the urine of other patients on the same diet

Further investigation showed that the new substance was detectable only after the urine had been electrolytically desalted, and that its colour was discharged by acetic acid but restored by ammonia Mineral acids and caustic alkalis destroyed the material, and its colour faded appreciably during drying of the chromatograms A second minor spot appeared when large quantities of urine were chromatographed in phenol-ammonia Some of the major coloured compound was eluted from the chromatograms with 50% aqueous acetone, although it was not soluble in water or acetone alone Evaporation of the eluate produced a pale-pink residue, which turned an intense reddish-

TABLE II—CLINICAL DETAILS OF 7 CASES OF MALE IMPOTENCE

Case	At time of original consultation			Outcome
	Husband's age (yr)	Duration of marriage (yr)	Duration of impotence	
1	28	3½	Throughout marriage	Conception during 3rd course of inseminations
2	36	2½	Throughout marriage	Conception during 7th course of inseminations
3	33	4	Last 3 yr of marriage	Conception during 4th course of inseminations
4	26	2	Throughout marriage	Insemination abandoned after 2nd month
5	27	1½	Throughout marriage	Conception during 3rd course of inseminations
6	40	7	Throughout marriage	Conception during 10th month of inseminations
7	31	5	Throughout most of marriage	Conception during 4th month of inseminations

Again the results suggest that insemination, under these circumstances, does not increase the likelihood of conception.

Male Impotence

These were the most successful cases in the whole series—6 out of 7 women became pregnant by insemination (table II). The 7th husband experienced difficulty in producing a specimen of semen for insemination, and after two months decided to discontinue the attempt. All 6 pregnancies resulted in normal children. 4 of the 6 men whose wives became pregnant were subsequently able to achieve a normal sexual relationship—in 2 cases during the pregnancy, and in the other 2, within six months of the birth of the child. The following histories illustrate a number of points common to many.

THE FIRST CASE

Husband and wife were well educated and intelligent. At the beginning of the marriage, the husband experienced difficulty in having intercourse due to, he thought, the use of a sheath contraceptive. This was exchanged for a vaginal occlusive pessary, and for six months intercourse was satisfactory. The husband then began, once more, to have difficulty in achieving and maintaining an erection, and, by the end of the first year of marriage, he was impotent and had lost all desire for intercourse. Six months later he was referred by his general practitioner to a psychiatric department. He attended at intervals over the next eighteen months, and was successively under the care of four different psychiatrists. Just when he felt that he was making progress he would find himself under the care of a new doctor. At the end of eighteen months there was no improvement in the impotence.

When seen at the infertility clinic, they had been married four years. Investigations revealed no abnormality, apart from the husband's impotence. Insemination was agreed upon and conception took place during the fourth month of treatment. The pregnancy had a noticeable effect on the husband. Within three months of conception he had resumed normal sexual relations with his wife. Two years after the birth of the child, marital relations were still normal (case 3, table II).

THE SECOND CASE

Two years before marriage the husband had attempted unsuccessfully to have intercourse with another woman. He was very conscious of this failure and had no hesitation in blaming this experience for his subsequent impotence. For the first six months of the marriage he was completely impotent, but a gradual improvement took place over the next year so that he was sometimes able to effect penetration but never to achieve an orgasm. A herniorraphy operation eighteen months after marriage was followed by a recurrence of the impotence, and this continued until the couple were seen at the infertility clinic, five years after marriage. Investigations revealed no significant abnormality in husband or wife and insemination was agreed upon. Conception took place during the fourth month's course of inseminations.

The husband's impotence continued throughout the pregnancy, but, three months after the birth of their child, normal sexual relations were achieved. Nine months after the birth of this child, a normal conception took place, but this pregnancy ended in abortion at the tenth week. A year after the abortion, sexual relations were then quite satisfactory (case 7, table II).

Hypospadias

Both men in this group had severe degrees of hypospadias, and, although intercourse was possible, there was complete inability to deposit semen in the vagina. Semen quality was excellent in each case, and insemination was successful in the fourth and seventh months respectively.

Bilateral Epididymal Cysts with Blockage of Vasa

Each of the 2 men had azoospermia, associated with bilateral epididymal cysts and blockage of the epididymides. Fluid containing motile spermatozoa was obtained from these cysts and used for insemination. The 1st couple, after seven months, decided to adopt a child.

The 2nd husband was offered surgical treatment by a colleague who carried out a vasoepididymal anastomosis, but spermatozoa did not appear in the semen. Fluid from the other cyst was used for insemination over a period of ten months until the cyst fibrosed and the treatment had to be abandoned.

Negative Postcoital Tests

In both cases, routine investigations on husband and wife showed no abnormality yet repeated postcoital tests revealed no spermatozoa in the vagina. Husband and wife were adamant that intercourse was normal, and usually accompanied by a male orgasm. One couple had been married for two and the other for four and a half years. Neither husband had any difficulty in producing specimens of semen which were shown to be highly fertile. In one case insemination was successful in the third month and, in the other, in the fourth month of treatment.

A 3rd couple, similar in every way, are at present under treatment. Insemination has been going on for seven months, so far without success.

Complications

Significant complications have, on occasions, been encountered. Between 1947 and 1950, when intracervical insemination was used, several women complained of colicky lower abdominal pain for several hours after 0·1 to 0·2 ml. of semen had been placed in the cervical canal. In one or two instances the patients felt sick or vomited and had to remain in bed for twelve hours. One patient developed an acute cervicitis, and another an acute salpingitis. Fortunately, both responded to antibiotic therapy. Intracervical insemination was stopped after these two incidents and no complications have been noted since then.

Conclusions

This small series shows that insemination with husbands' semen has a limited but important place in the management of childlessness. Conception is most likely to follow insemination when husband and wife are fertile but the husband is incapable of depositing semen in the vagina. It is encouraging to find that pregnancy, under these circumstances, can help husband and wife achieve a normal sexual relationship.

Impotence can take other less obvious forms. It may appear from the clinical history that the sexual act is normal in every way, yet repeated postcoital tests show that there is no ejaculation of semen into the vagina. This type of coital failure is probably unusual, but lesser degrees, where the husband fails to ejaculate on many occasions, may be more common than is generally suspected. Insemination will increase the likelihood of conception in these cases.

When semen quality is poor, there is no evidence that insemination improves the chance of conception. These couples are best advised to continue their normal sexual relationship, for there is good evidence that, even with severe oligospermia, intercourse can result in conception and successful pregnancy (Harvey and Jackson 1948, White and Barton 1951, Russell 1954).

I am grateful to Mr Keith Yeates of the Newcastle General Hospital for his help in dealing with one of the men with bilateral epididymal cysts and azoospermia.

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TREATMENT OF THE NASAL CARRIER OF STAPHYLOCOCCUS AUREUS WITH FRAMYCETIN AND OTHER ANTIBACTERIALS

BRYAN STRATFORD
M.B. Melb.
DEPUTY MEDICAL SUPERINTENDENT, ST VINCENT'S HOSPITAL, MELBOURNE

SYDNEY D. RUBBO
M.D. Melb., Ph.D. Lond., Dip. Bact.
PROFESSOR OF BACTERIOLOGY IN THE UNIVERSITY OF MELBOURNE

R. CHRISTIE
M.Sc. Melb.
BACTERIOLOGIST, ST VINCENT'S HOSPITAL, MELBOURNE

SHIRLEY DIXSON
RESEARCH OFFICER, SCHOOL OF BACTERIOLOGY, UNIVERSITY OF MELBOURNE

THERE is general agreement that the healthy nasal carrier of *Staphylococcus aureus* constitutes one important reservoir of infection. Since many different phage-types are responsible for endemic staphylococcal disease in hospitals, it is impossible to distinguish between benign and dangerous carriers (Williams 1959). Accordingly, one is forced to regard all carriers as potentially dangerous (Elek 1959). When an outbreak of staphylococcal infection is traceable to a particular phage-type—e.g., 80/81—the detection of the dangerous disperser is greatly simplified, but this ideal epidemiological situation is seldom found in endemic hospital cross-infections affecting adults.

A reduction in the number of nasal carriers of staphylococci cannot be brought about by the use of antibacterial nasal toilet alone, as the nasal mucosæ are continually exposed to reinfection by airborne organisms. The more widespread the environmental contamination, the higher the nasal carrier-rates among staff and patients. If, however, the endemic balance between primary and secondary sources of infection could be reduced, then the chances of acquiring clinical infection should be lower—assuming, of course, that there was no change in virulence of the organism and no lowering of resistance of the patient.

We are here concerned with the treatment of the nasal carrier. We have compared a number of recommended preparations—firstly as regards the rate of suppression of nasal carriage, and secondly, the success-rate after seven days of treatment. Recolonisation of the cleared carriers was sought, but this is as much an index of environmental exposure as a measure of the efficacy of nasal toilet.

Of the two methods of applying these preparations, we have found the aqueous spray generally more effective than the corresponding ointment (or cream). Doubtless the ointment remains longer in contact with the mucosal surface, but it seldom reaches sites of possible colonisation that are beyond the vestibule of the nose.

We have always used a ' deep nasal swab ' for detection of nasal carriers in preference to the commonly used " shallow swab " of the anterior nares. In a survey of 103 patients, deep swabbing yielded a higher proportion of positive carriers. As the success of any preparation depends on contact with the infecting organism, deeply and liberally applied sprays must carry a greater chance of success than a cream applied to the anterior nares.

Materials and Methods

Nasal swabbing.—To have a sound basis for selecting nasal carriers, two types of swabs were taken in a group of 103 patients at the one visit. The first swab was made from the vestibule of each nostril, that is, an anterior nasal swab, and the other from the vestibule to a point just below the middle turbinate, that is, a deep swab (fig. 1). In each case the swab was rotated through three full turns during the operation of swabbing. The deep-swab technique should be done by a person familiar with the internal anatomy of the nasal cavity. All swabs were plated on blood-agar media, incubated for twenty-four to forty-eight hours at 37°C. *Staph. aureus* was identified on colony form, and on pigment and coagulase production.

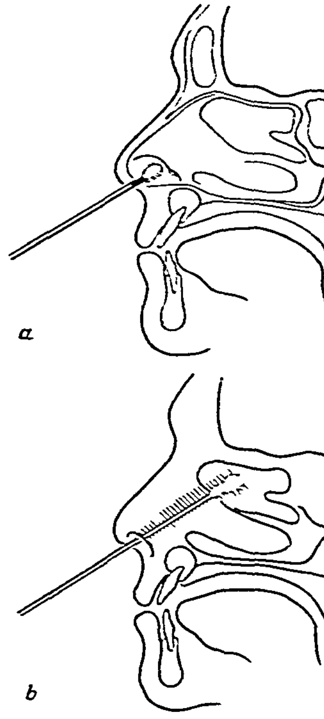

Fig. 1—*a*, area sampled in anterior nasal swab. *b*, area sampled in deep nasal swab.

Nasal preparations.—The products used were:

a. 'Neotracin' ointment containing neomycin 5 mg., polymyxin 5000 units, and bacitracin 500 units per g.

b. Neomycin spray containing neomycin 2 mg. and polymyxin 5000 units per ml.

c. Naseptin ointment containing chlorhexidine hydrochloride ('Hibitane') 0·1%, and neomycin 0·5%.

d. Chlorhexidine-neomycin spray in saline containing the same concentration of active ingredients as naseptin.

e. Soframycin ointment containing framycetin 1·5% and gramicidin 0·005%.

f. Soframycin spray containing framycetin 1·25% and gramicidin 0·005% in isotonic solution containing phenylephrine hydrochloride 0·25% as a vasoconstrictor.

g. Soframycin spray as (f) but without the vasoconstrictor.

The ointments were applied with a swab to the anterior nares. The sprays were instilled into the nasal cavity, under pressure, from plastic containers in such quantity that some of the liquid passed to the back of the patient's throat. All patients were treated individually by one or other of us. Each preparation

CHROMATOGRAPHIC PROPERTIES OF PIGMENT DERIVED FROM "T-SUBSTANCE"

—	Rf values obtained in parallel runs		
	Phenol ammonia	Butanol butanone-dicyclohexyl-amine-water (10/10/2/5)	Butanol 2N-*ammonia* (1/1, upper phase)
Desalted urine of patient	Major spot 0·47 Minor spot 0·81	(0·24) (0·42)	0·09
Normal urine containing 1% alloxan (desalted)	Major spot 0·48 Minor spot 0·79	(0·27) (0·44)	0·08

purple when exposed to ammonia, in much the same way as murexide.

This suggested that the anomaly might be due to a disorder of purine metabolism, and attempts were made to reproduce the formation of the coloured compounds by adding various purines and related substances to normal urines, which were subsequently desalted and chromatographed. The only substance which behaved similarly proved to be alloxan, the spots obtained were chromatographically indistinguishable from those produced by the patient's urine (see table).

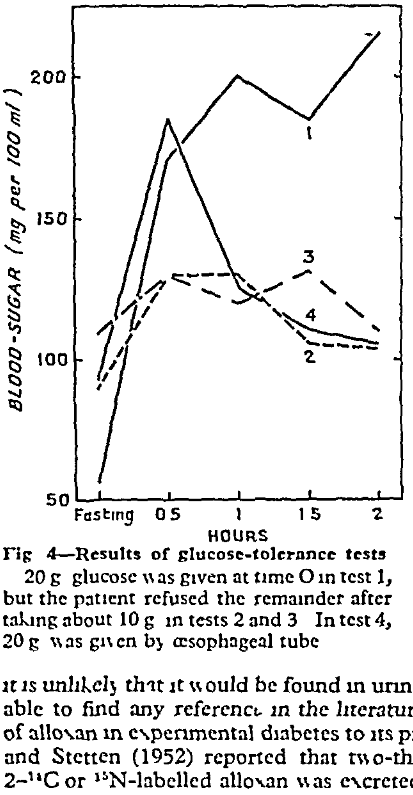

Fig. 4.—Results of glucose-tolerance tests.

20 g. glucose was given at time O in test 1, but the patient refused the remainder after taking about 10 g. in tests 2 and 3. In test 4, 20 g. was given by œsophageal tube.

Because of the unexpected similarity of T-substance to alloxan, a glucose-tolerance test was carried out and gave the result shown in fig. 4 (1). Subsequent tests, however, have given completely normal curves (fig. 4—2, 3, and 4), and the child's urine has remained free from reducing substances.

Since alloxan is highly unstable under neutral and alkaline conditions it is unlikely that it would be found in urine. We have been unable to find any reference *in the literature* on the metabolism of alloxan in experimental diabetes to its presence in urine. Lee and Stetten (1952) reported that two-thirds of administered 2-^{14}C or ^{15}N-labelled alloxan was excreted by rats and rabbits within 3 days, but were unable to detect alloxan in the urine.

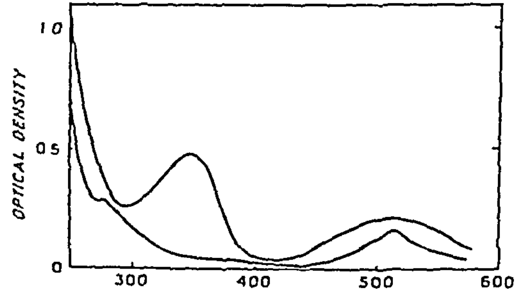

Fig. 5.—Ultraviolet absorption-spectrum of pigment eluted from chromatograms of electrolytically desalted urine from patient (lower curve) compared with that of murexide prepared by treating alloxantin with ammonia in ethanol (upper curve).

Comparison of the ultraviolet absorption-spectrum of the pigment derived from T-substance with that of murexide, prepared by treating alloxantin with ammonia in 50% ethanol, showed that there is similarity in the visible region only (fig. 5). Another difference is that T-substance is extractable into *n*-butanol at pH 5, whereas alloxan is not. After removal of the solvent, the extract was dissolved in water and electrolytically desalted. The resulting solution gave the red spot when chromatographed in phenol-ammonia.

We tried to determine whether the abnormal substance appearing in the urine was the result of the metabolism of exogenous or endogenous purines. The child was given a virtually purine-free diet containing milk, cheese, and eggs, and the spot disappeared from his urine chromatograms. It did not reappear when the purine bases caffeine, adenine, guanine, xanthine, and the pyrimidine bases cytosine, thymine, and uridine, in daily doses of 100 mg. were added to the diet, but, when a normal diet was reintroduced, the spot returned. We are indebted to Dr. Mary L. Efron, of University College Hospital Medical School, for examining specimens of urine by high-voltage electrophoresis (Efron 1959). When the patient was first under investigation, Dr. Efron reported that no uric acid could be detected, but, in later samples of urine, small quantities were found. Subsequently serum and urine uric acid levels (determined colorimetrically) became normal, except when the patient was placed on a diet low in purines.

Discussion

Since the advent of relatively simple methods of examining the serum and urine for abnormal substances, a growing diversity of genetically determined metabolic errors has been described, there are at least 50 well-authenticated deviations (Hsia 1959). The abnormality we describe is interesting because it appears to be the first anomaly of purine breakdown, other than uricæmia. Intensive chemical analyses have not so far identified this substance, but there are good grounds for believing it is closely related to alloxan. Alloxan is an oxidation product of uric acid, and it may well be that in our case there is an abnormality in uric-acid formation which results in the accumulation of T-substance. This may have poisonous effects when formed in sufficient quantities. Two of the four subjects excreting large amounts of T-substance or similar compounds, are grossly retarded physically and mentally, a third child is small for her age, weighing only 20 lb. at 5 years. The fourth child, a brother of the last, is, as far as we can ascertain, normal in all respects other than the excretion of T-substance. The family tree of our patient shows that the abnormality is inherited as an autosomal recessive, since both parents excrete the substance in small amounts, but do not seem to be disabled apart from acquired disease. Many of the ascendants and collaterals also excrete the substance in small quantities, but without overt ill effects. The observation that females may excrete T-substance in large quantities suggests that they may also be affected, and seems to discount the possibility that the gene is carried on the X-chromosome.

An important, but still unanswered, question is whether this metabolic defect is directly related to the abnormalities observed in three of the four homozygous children. As far as we can find out, there is no other obvious explanation for their gross physical defects, and we must infer that this is the cause of their disabilities. It has been impossible, at the time of writing, to find out whether the substance excreted is present in the serum, but it probably accumulates in the blood, and there is a threshold level *above which it appears in the urine*. This would explain the disappearance of T-substance from the urine during the short periods in which the child received a purine-free diet, and suggests that T-substance may be entirely related to exogenous purine metabolism

Summary

Clinical and biochemical details of a child, aged 4, who excretes a hitherto undescribed substance in his urine are presented This abnormal urinary constituent, still unidentified and called provisionally T-substance, is also excreted in much smaller amounts by many members of the child's family The metabolic defect appears to be transmitted as an autosomal recessive characteristic The child is both physically and mentally retarded

Two other children—unrelated to the first—have been discovered who excrete T-substance in equivalent amounts and are believed to be homozygous for the abnormal gene one of these is physically, but not mentally, retarded A fourth child who is physically and mentally backward also excretes a similar substance

T-substance is apparently an abnormal product of purine metabolism, chemically related to, but not identical with, alloxan

It is a pleasure to express our thanks to Mr D R W Rawson, technician, who first drew attention to this peculiarity, and carried out much of the technical work, to Dr C S Ayoub, lately registrar at Westminster Children s Hospital, and to Dr P V Hunt and Dr P Boardman, house-physicians, for the care and hard work they have bestowed upon the patient Also to Sister M Parker and the nursing staff of Muriel Lesley Gamage ward, without whose skilled nursing the metabolic studies could not have been undertaken

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ARTIFICIAL INSEMINATION (HUSBAND) IN THE MANAGEMENT OF CHILDLESSNESS

J K Russell
M D Aberd, F R C O G
PROFESSOR OF OBSTETRICS AND GYNÆCOLOGY,
KING'S COLLEGE, UNIVERSITY OF DURHAM

MOST gynæcological departments in the larger hospitals in this country have special clinics for the investigation and treatment of childlessness, but little is known of the use that they make of artificial insemination with husbands' semen There is scant information about the extent of the practice, the type of case selected for insemination, the chance of success, or the likelihood of complication More attention has been paid to donor insemination, with its ethical and legal overtones, but, here again, there is little factual information My own experience of insemination is not extensive, and is limited to cases in which husbands' semen has been used Since 1946, I have examined 1400 married couples whose complaint has been involuntary childlessness In 55 of them, artificial insemination with the husbands' semen has been given serious trial

Technique of Insemination

The courses of insemination often extended over several months Each course consisted of three inseminations, carried out on the twelfth, fifteenth, and eighteenth days of the cycle The shortest course lasted two months and the longest was continued intermittently for two years

Semen was obtained from the husbands under standard conditions They were advised to avoid intercourse for three days before producing the specimen, which was placed directly into a small sterile glass jar, specially provided for the purpose

TABLE I—DATA ON 55 CASES OF ARTIFICIAL INSEMINATION

Reason for insemination	No of patients	No of patients who conceived during treatment	Remarks
Oligospermia (spermatozoon-counts below 10 million per ml)	34	2	8 of these patients subsequently conceived without insemination With 1 exception all the pregnancies terminated successfully
Apparent cervical hostility	8	1	2 patients conceived some time later without insemination All 3 pregnancies were successful
Male impotence	7	6	Each of the 6 pregnancies produced a normal child
Hypospadias	2	2	Both pregnancies were successful
Bilateral blockage of vasa with epididymal cysts	2	0	Spermatozoon counts varied from 5 to 20 million per ml in each case
Negative postcoital tests	2	2	Both husbands were highly fertile The pregnancies were uncomplicated

In the early cases, 0 1–0 2 ml of semen was placed into the lower part of the cervical canal The semen was never more than two hours old A sterile 1 ml syringe and a long wide-bore needle with a blunt point were used for the purpose In 1950, intracervical insemination was discontinued and thereafter 0 5–2 ml of fresh semen was sprayed round the external cervical os For half an hour after insemination the patient remained at rest on her back with the buttocks slightly raised

Results

Husband and wife had previously had routine investigations carried out in the departmental infertility clinic and full medical histories were available There were a variety of indications for insemination—some female, others male (table I)

Oligospermia

Each of the 34 husbands in this group had a spermatozoon-count consistently below 10 million per ml and, so far as could be ascertained, this was the only apparent reason for the childlessness

The shortest course of insemination in this group was seven months and the longest (with two months missed) was two years 2 of the women became pregnant, the 1st after eleven months' and the 2nd after eighteen months' treatment Both pregnancies were uncomplicated and produced normal children

In following up this group of 34 women, it was discovered that 8 of them had subsequently conceived without insemination and that 7 successful pregnancies had resulted Where poor-quality semen appears to be the cause of childlessness, there is nothing to suggest that insemination improves the chance of conception Indeed, it may have the opposite effect for it is quite likely that the artificial method by which the specimen is collected may further depress the semen quality

For the past few years in this department, oligospermia has not been accepted as an indication for insemination

Apparent Cervical Hostility

In each of the 8 cases, repeated postcoital examinations revealed only dead spermatozoa in the cervical mucus, in spite of the fact that the husbands all had excellent semen specimens No obvious abnormality had been found in any of the women at the infertility clinic 1 patient conceived during treatment, another 2 became pregnant some time after the inseminations had been discontinued

TABLE I—COMPARISON OF ANTERIOR AND DEEP NASAL SWABBING OF 103 PATIENTS IN HOSPITAL

Type of swabbing	Nasal carriers detected	
	Number	Carrier rate
Anterior	35	34%
Deep (see text)	53	51%

was tested in 20 patients, each of whom was shown to have more than twenty colonies of *Staph aureus* on plating of a deep swab On every occasion, the patient was swabbed immediately before treatment, two hours after the first application, and afterwards daily for seven days Medication then ceased, but daily swabbing was continued for at least twenty-one days, or for a shorter period if the patient was discharged from the hospital

Results

A significant difference in the number of detectable nasal carriers can be shown after shallow (anterior nasal) and deep (anterior and middle nasal) swabbing Table I shows the results obtained on 103 patients, and emphasises the importance of taking a deep nasal swab

Table II summarises the results of treatment of groups of nasal carriers with the different preparations

In this table we have listed the results obtained twenty-four hours, and seven days respectively after the beginning of treatment The soframycin spray was outstandingly more successful after twenty-four hours than any of the other preparations The inclusion of a vasoconstrictor in this spray appeared to improve its antibacterial action over a period of seven days The fluted nebuliser in which the soframycin spray is dispensed may contribute to its success About 2 ml of fluid is ejected, first as a coarse spray and then as a fine jet On the figures recorded here, one application of soframycin spray suppressed nasal staphylococci in 85% of nasal carriers In fact, approximately 80% of carriers are cleared within two hours of the first application of the spray No other product in this series was so effective Daily treatment for seven days with soframycin spray cleared all carriers in our series Of the other preparations, chlorhexidine-neomycin spray appeared to be the next most efficacious, but was considerably less so than soframycin

TABLE II—RATE OF CLEARANCE OF *Staph aureus* BY VARIOUS PREPARATIONS

Preparation	Frequency of application	Number treated	Number cleared (negative swab) after	
			24 hours	7 days
Soframycin spray with vasoconstrictor	once daily	20	17 (*85%*)	20 (*100%*)
Soframycin spray without vasoconstrictor	once daily	20	17 (*85%*)	17 (*85%*)
Soframycin ointment	twice daily	20	5 (*25%*)	18 (*90%*)
Chlorhexidine-neomycin spray	once daily	20	5 (*25%*)	15 (*75%*)
Naseptin ointment (chlorhexidine-neomycin)	twice daily	20	1 (*5%*)	9 (*45%*)
Neomyxin spray	*once daily*	20	7 (*35%*)	10 (*50 %*)
Neotracin ointment	thrice daily	20	4 (*20%*)	13 (*65 %*)

The remarkably rapid rate of clearance induced by soframycin in this series was investigated further using 85 nasal carriers, who were treated twice with the spray at twenty-four hour intervals The results of this short treatment are shown in fig 2

It will be seen that 76% of the carriers were cleared within two hours after one application of the spray, and all were free of staphylococci after the second application The antibiogram patterns of a number of staphylococci were done, and most of the strains were resistant to penicillin, streptomycin, and the tetracyclines, in other words, they were typical of the "hospital staphylococcus"

Reinfection of the nasal mucosæ after clearance occurred with all preparations Table III shows that approximately 50% of the cleared carriers reverted to the carrier state after cessation of treatment, but the time taken to revert after soframycin was clearly different from that found with the other preparations With the latter, the staphylococcus free state lasted, on an average, two days, whereas after soframycin treatment an average of seven to fourteen days elapsed before reversion Since all patients were exposed to the same degree of airborne infection, it would appear that the soframycin-treated group were reinfected from exogenous sources, whereas the reversion in other carriers was mainly endogenous Elimination in the soframycin-treated group was bacteriologically complete, but incomplete with the other preparations Unfortunately, phage-typing of isolates was not available to confirm this interpretation, which, if correct, provides a further reason for recommending soframycin spray for treatment of the nasal carrier

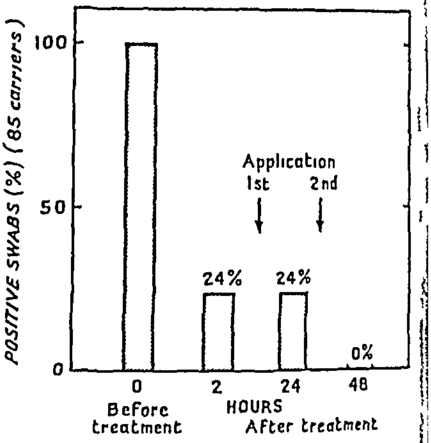

Fig 2—Suppression of nasal carriage of *Staph aureus* by treatment with soframycin nasal spray

Discussion

A vast literature dealing with the nasal carriage of *Staph aureus* has appeared during the past decade

Some authors, e g , Gould and Cruikshank (1957), Williams (1959) have suggested that acquired staphylococcal infections —as many as 80% of them according to Gould (1957)—might result from autoinfection Williams et al (1959) proved that "patients who were or became nasal carriers of staphylococci had three times as much staphylococcal sepsis as those who were never carriers" Further, it appeared "that self infection is important in the ætiology of the septic lesions" In a study of postoperative surgical infections in tuberculous patients subjected to elective chest surgery, Weinstein (1959) reported that, of patients with positive nose-cultures for *Staph aureus*, 37% exhibited postoperative infected complications, whereas

TABLE III—RECOLONISATION OF NASAL MUCOSÆ WITH *Staph aureus* AFTER SUCCESSFUL TREATMENT

Preparation	Number of patients	Number recolonised	Average time of recolonisation after cessation of treatment (days)
Soframycin spray with vasoconstrictor	20	10 (*50%*)	14
Soframycin ointment	18	10 (*55%*)	7
Chlorhexidine neomycin spray	15	8 (*55%*)	2
Naseptin ointment (chlorhexidine-neomycin)	9	4 (*44%*)	2
Neomyxin spray	10	5 (*50%*)	2

among the group with negative nose cultures, 11% had infected complications

These findings suggest that the suppression of nasal carriage would be a useful measure before elective surgery, particularly in patients who are admitted to hospital some time before operation Recent work by Gillespie et al (1959) indicates, however, that the suppression of nasal carriage will not necessarily reduce the overall incidence of cross-infection in general hospitals Environmental contamination can arise from primary reservoirs other than the nose—for example, the perineum (Hare and Ridley 1958), skin and clean infected wounds (Gillespie et al 1959), all of which maintain the staphylococcal infection cycle Silent nasal colonisation and the hazard of autoinfection inevitably follow Nevertheless, any plan for effective reduction of staphylococcal disease in hospitals must be broadly based, and the suppression of nasal carriers by topical chemotherapy is only one of a number of measures which must be considered in the epidemiological control of this disease

The present study was designed to provide information on an administratively simple and clinically effective treatment of nasal carriers in hospital Thus, in comparing various preparations, it is only fair to state that we intentionally did not follow the manufacturer's directions if these were considered too complex for practical use We were mainly concerned with discovering some preparation which could suppress nasal carriage in the shortest possible time The test for suppression in this study was more rigorous than in most, since all observations were based on the deep swabbing technique (fig 1) This method detected 17% more nasal carriers than swabbing the anterior nares (table I)

Soframycin spray was outstandingly the most successful preparation (table II) When a larger number of nasal carriers was treated, it was found that all carriers yielded negative cultures in forty-eight hours—that is, after two applications of the spray (fig 2) Furthermore, it appeared that clearance of nasal staphylococci by soframycin was more complete than by other methods of treatment, since recolonisation of the mucosæ was significantly slower (table III) The success of soframycin spray is attributable largely to its bactericidal action Experiments, not reported here, showed that soframycin killed *Staph aureus*, resistant to many antibiotics, in less than a minute in the presence of 50% serum

This work is now being extended to determine whether intermittent use of soframycin spray will decrease the nasal-carriage rate, and thus indirectly lower the environmental contamination We hope that this proposed extension of the present study will provide a basis for control of the nasal carrier which does not impose too many demands on the nurses

Summary

The treatment of the nasal carrier of *Staphylococcus aureus* by chemotherapeutic agents was investigated The emphasis in this study was on the rate of clearance as well as the success after seven days' treatment

The results indicate that, in general, atomised spray preparations are more effective than the corresponding ointments

Of the preparations compared, 'Soframycin' spray, containing framycetin and gramicidin as antibacterial agents, was the most effective With this spray, approximately 80% of nasal carriers were cleared in twenty-four hours (that is, by one application only), and 100% after two days' treatment

The importance of deep nasal swabbing for detecting nasal carriers has been demonstrated

We wish to thank the National Health and Medical Research Council, and the Hospitals and Charities Commission of Victoria for financial assistance We are grateful to the Mother Rectress who kindly allowed these studies to be made in St Vincent's Hospital Roussel Laboratories, Imperial Chemical Industries of Australia and New Zealand, and Andrews Laboratories supplied the nasal preparations

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SCARLET-FEVER-LIKE ILLNESS DUE TO STAPHYLOCOCCAL INFECTION

WILLIAM N DUNNET
M B Aberd, D P H
SENIOR REGISTRAR, INFECTIOUS DISEASES UNIT

EVELYN M SCHALLIBAUM
M B Lond
SENIOR REGISTRAR, BACTERIOLOGY

ROYAL FREE HOSPITAL, HAMPSTEAD, LONDON, N W 3

AN illness resembling scarlet fever, but caused by *Staphylococcus pyogenes*, has been described on several occasions (Stevens 1927, Mackenzie 1934, Zinsser et al 1939, Aranow and Wood 1942, Negro et al 1956) We report three more cases

Case-reports

Case 1—A woman, aged 20, was admitted on Nov 26, 1942, with the provisional diagnosis of scarlet fever Six days before admission, she had a left axillary abscess, and, on the day of admission, a scarlatiniform rash appeared on the neck, trunk, and limbs There was a history of measles, rubella, and pertussis in childhood, but of no other specific infections The temperature was 102°F, pulse-rate 118 There was a large abscess in the left axilla The fauces were mildly injected, but there was no exudate

Investigations—Culture of pus from the abscess gave a pure growth of *Staph aureus* The hæmolytic streptococcus was not isolated from repeated nose and throat swabs The total white-cell count was 16,000, with a neutrophil leucocytosis

Treatment—The abscess was incised, and 20 ml scarlatinal antitoxin was administered intramuscularly A course of sulphanilamide, totalling 21 g, was given

Progress—The pyrexia subsided on the sixth day The tongue peeled and the rash faded on the third day, thereafter, desquamation began, particularly on the palms and soles When discharged on Dec 17, the soles were still peeling

Case 2—A woman, aged 21, was admitted on Feb 12, 1958, with a provisional diagnosis of septic abortion Three days before admission, there had been vaginal blood-loss with diarrhœa and vomiting Two days later, the patient aborted A rash appeared on the trunk on the day of admission There had been two normal pregnancies, but no previous miscarriages The last menstrual period had been three months previously, the patient had suffered from nausea and vomiting, and had not felt really well during the pregnancy There was a past history of measles only and there had been no contact with recent infectious disease

The patient looked ill and toxic There was a bright erythema on the trunk and limbs The fauces and buccal mucosa were red, but there was no exudate Several small cervical lymph-nodes were palpable The blood-pressure was 100/70 mm Hg The size of the uterus corresponded to three months' pregnancy Offensive placental fragments protruded through the os

Investigations.—Culture of high vaginal and cervical swabs gave a pure growth of *Staph. pyogenes*, resistant to penicillin, but sensitive to chloramphenicol, streptomycin, the tetracyclines, and erythromycin. Culture of nose, throat, and post-nasal swabs also yielded a moderate growth of *Staph. pyogenes* with the same sensitivity. The urine contained a trace of albumin, pus cells, red cells, and granular casts, and coliform bacilli were grown on culture. Culture of the fæces was negative. Blood-culture was negative. The white-cell count was 12,000, with a neutrophil leucocytosis. The serum-potassium, serum-sodium, and serum chlorides were 3.2, 132, and 95 mEq per litre respectively. The blood-urea was 115 mg. per 100 ml. The Wassermann reaction and the Kahn test were negative. *Treponema pallidum* was absent from three preparations from the mouth lesion. The gonococcal complement-fixation test was negative. The Dick test and the Schultz-Charlton test, done on admission, were both negative.

Treatment.—Fluids and electrolytes were administered by continuous intravenous drip. The patient was given crystalline penicillin, 500,000 units six-hourly. When the sensitivity reaction showed the organism to be penicillin-resistant, the drug was discontinued after 1.5 megaunits had been given, and tetracycline was administered orally, 750 mg. six-hourly, to a total of 10.5 g. An infection of the mouth due to *Candida albicans* then developed, and the tetracycline was discontinued. Nystatin, 250 mg. six-hourly, to a total of 5 g., together with local crystal violet effectively controlled this, but on Feb. 25, multiple furuncles appeared on the perineum and buttocks, and, five days later, on the right hand. Intramuscular streptomycin, 1 g. twice daily to a total of 13 g., was given, together with erythromycin, 250 mg. six-hourly, to a total of 6.5 g.

Progress.—Fever continued for twenty days, with temperatures up to 103°F. After a week, the blood-urea had fallen to 26 mg. per 100 ml., and the electrolytes were normal. The rash faded after three days and desquamation began on the seventh day, particularly on the hands, arms, and soles. When the patient was discharged on March 7, the uterus had involuted normally and the adnexa were clear. All the staphylococcal lesions had healed, apart from one boil on the thumb from which there was still a slight discharge.

Case 3.—A girl, aged 19, was admitted on April 28, 1959, with a provisional diagnosis of scarlet fever. Eleven days previously she had a boil in the right axilla, and two days before admission complained of headache, stiffness in the wrists and fingers, and sore heels. On the same day, a rash appeared on the hands, spreading to the legs and arms next day. There was a history of chickenpox and pertussis only in childhood. There had been no recent contact with infectious disease.

The patient looked toxic, had frank rigors, and was faintly jaundiced. The temperature was 103.6°F, pulse-rate 136, and blood-pressure 100/50 mm. Hg. There was a bright punctate erythema involving the trunk and limbs with definite folliculitis on the trunk. The fauces were red, the tonsils small and injected, but there was no exudate. The tongue was furred. Small lymph-nodes were palpable in the anterior triangles of the neck. There was a small, tense abscess in the right axilla. Both wrists were slightly swollen and hot, and there was some swelling of the proximal interphalangeal joints of the fingers of both hands.

Investigations.—The white-cell count was 26,800 (polymorphs 95%). Platelets 120,000 per c.mm. The erythrocyte-sedimentation rate (E.S.R.) was 45 mm. in the first hour (Westergren). In the corpuscle-fragility test, hæmolysis began at 0.45%, and was complete at 0.36%. The urine contained urobilin and urobilinogen in excess. The total serum-proteins were 6.1 g. per 100 ml. (albumin 3.6 g. per ml., globulin 2.5 g. per ml.). The direct van den Bergh test was positive. Total serum-bilirubin was 5.0 mg. per 100 ml. The liver-function tests were normal. Culture of pus from the abscess showed a heavy growth of *Staph. pyogenes*, phage-type 29. The hæmolytic streptococcus was not isolated from cultures of nose, throat or post-nasal swabs. Blood culture was negative. The Dick test and the Schultz-Charlton test, done on admission, were both negative.

Treatment.—Crystalline penicillin, 500,000 units six-hourly, was given initially, but this was replaced by tetracycline, 750 mg. six-hourly orally, when the sensitivity pattern showed the staphylococcus to be penicillin-resistant.

Progress.—On the second day after admission, the patient was jaundiced and the rash was more pronounced. The axillary abscess ruptured spontaneously and discharged thick pus. The pyrexia abated on the fourth day, and the jaundice lessened. Peeling began on the palms and soles, and next day there was generalised desquamation. The joints were no longer swollen. By the tenth day, the desquamation was complete and the tongue was clean. The total serum-bilirubin was 0.5 mg. per 100 ml., and the direct van den Bergh test negative. The E.S.R. had fallen to 8 mm. The patient was discharged on the fourteenth day after admission, symptom-free. The axillary abscess had completely resolved.

Two months later, the patient was readmitted with a recurrence of axillary boils, but on this occasion there was no rash and no jaundice.

Investigation of the Staphylococcal Filtrate

A sterile filtrate was prepared from the staphylococcus isolated from case 1, and intradermal tests were done using (1) the filtrate alone, (2) the filtrate combined with scarlatinal antitoxin, and (3) the filtrate combined with staphylococcal antitoxin. The results of the tests were inconclusive.

A filtrate of the staphylococcal culture from the axillary abscess of case 3 was also prepared by the method described for the Dick toxin (Dick and Dick 1938). Dilutions of this filtrate, 1/10 to 1/10,000, were made, using a buffer solution. Intradermal tests on Dick-positive subjects, using these dilutions, were then carried out.

Our method of doing the intradermal test is to raise a button, approximately 5 mm. in diameter, at the site of injection. We have found by experience that injecting a fixed quantity of toxin does not mean that this amount will necessarily get into the tissues because there is usually leakage around the needle.

Dilutions of 1/100 gave a bright erythematous reaction, about 10 mm. in diameter, in susceptible patients. The reaction began four to six hours after injection and was maximal in twelve to eighteen hours.

After heating the filtrate to 100°C for sixty minutes, there was no reaction when it was injected intradermally into susceptible subjects. This preparation was used as a control in the subsequent experiments on 37 patients, chosen at random, suffering from diseases not associated with staphylococcal or streptococcal infection.

The staphylococcal filtrate (dilution 1/100) was injected intradermally into the anterior surface of the right forearm and the control into the left, the Dick toxin and control being administered vice-versa. An erythematous reaction measuring 5 mm. or more was regarded as positive, provided the control test was negative, or, where both were positive, the reaction to the toxin had to be appreciably larger than the control to be considered positive. The results are summarised in table I.

Of the 7 positive staphylococcal-toxin reactors, aged 2-5, 2 were Dick-negative, of the 9 in the group 6-15, 4 were Dick-negative. Both the patients in the over-15 group who were Dick-positive also reacted to the staphylococcal toxin.

TABLE I—REACTIONS TO DICK TOXIN AND TO STAPHYLOCOCCAL TOXIN (CASE 3) IN PATIENTS WITH DISEASES NOT ASSOCIATED WITH STAPHYLOCOCCAL INFECTION

Age (yr.)	Positive Dick reactors	Positive staphylococcal toxin reactors	Total
2-5	7	7	10
6-15	8	9	15
Over 15	2	6	12
Total	17	22	37

TABLE II—REACTIONS TO DICK TOXIN AND STAPHYLOCOCCAL TOXIN (CASE 3) IN 5 CASES OF SCARLET FEVER

Case	Sex	Age (yr)	Day of disease	Staphylococcal filtrate (1/100)	Staphylococcal control	Dick toxin	Dick Control
1	M	5	2	Positive	Negative	Positive	Negative
			12	"	"	Negative	"
2	F	4	2	"	"	Positive	"
			8	"	"	Negative	"
3	F	4	5	"	"	Positive	"
			12	"	"	"	"
4	M	8	2	Negative	"	Negative	"
			12	"	"		"
5	F	6	3	Positive	"	Positive	"
			13	"	"	"	"

Similar intradermal tests were done on 5 consecutive cases of confirmed scarlet fever (all of whom had a heavy growth of β-hæmolytic streptococci in the throat swabs) These tests were done on admission and were repeated the day before discharge The results are shown in table II

These results suggested that the erythrogenic toxin elaborated by the staphylococcus was probably antigenically different from that produced by the β-hæmolytic streptococcus This observation was confirmed to some extent by the fact that both the Dick and Schultz-Charlton tests were negative in cases 2 and 3 on admission, when one would have expected these tests to have been positive if the patient had scarlet fever

Discussion

Certain strains of *Staph pyogenes* can produce an erythrogenic toxin Pilot and Afremow (1927) prepared a filtrate from a staphylococcal culture which gave an erythematous reaction measuring 2-5 cm on intradermal injection They found that antitoxin serum, prepared by injecting the filtrate into rabbits, neutralised the skin reaction, but that this serum had no effect on the erythrogenic toxin produced by the hæmolytic streptococcus Stevens also noted in his cases that the rash was blanched by staphylococcal antitoxin, but was unaffected by the hæmolytic streptococal antitoxin

Satake (1927) isolated a hæmolytic *Staph aureus* from the throat of a patient with scarlet fever, in whom search for the hæmolytic streptococcus had proved fruitless He demonstrated an erythrogenic toxin in the filtrate from a culture of this staphylococcus, which produced a typical scarlet-fever syndrome when given in large doses to subjects whose skin reacted to the toxin

Reme (1930) found that 12 out of the 15 strains of hæmolytic staphylococcus tested yielded an erythrogenic toxin Mundt (1939) examined the filtrate from the cultures of 19 different strains of hæmolytic *Staph aureus*, and found that 10 of these strains yielded an erythrogenic toxin which produced a reaction similar to the Dick test in Dick-positive subjects She also showed that the addition of scarlatinal antitoxin neutralised the effect of this toxin These findings were substantiated by Aranow and Wood (1942) who isolated a *Staph aureus* from repeated blood-cultures of a patient with osteomyelitis in whom severe scarlatiniform eruption developed

In two of our patients (cases 2 and 3), where the Schultz-Charlton test was done on admission, there was no blanching of the rash when scarlatinal antitoxin was injected intradermally

Toxicity, a bright erythema, and profound desquamation were features of our three patients The jaundice in case 3 was undoubtedly caused by intravascular hæmolysis due to the severity of the infection It is surprising that the staphylococcus was not isolated from the blood-culture in this case, but only one culture was possible before starting antibiotic therapy

Summary

In three illnesses resembling severe scarlet fever the only pathogen found was the *Staph pyogenes* It was demonstrated, by intradermal tests on susceptible subjects, that the filtrate, prepared from the culture of the staphylococcus isolated from case 3, contained an erythrogenic factor This erythrogenic toxin may differ in its antigenic properties from that produced by the hæmolytic streptococcus

We should like to thank Dr William Gunn and Dr A M Ramsay for their encouragement and for access to the records of case 1 which was not seen by either of us We are also indebted to Dr R E O Williams, Staphylococcal Reference Laboratory, Colindale, for phage-typing the organism isolated from case 3 It is a pleasure to acknowledge our gratitude to Miss M E Beacock, librarian of the Royal Free Hospital

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RAPID DESTRUCTION OF ANTITETANUS SERUM IN A PATIENT PREVIOUSLY SENSITISED TO HORSE SERUM

MALCOLM P GODFREY
M B Lond , M R C.P
LATELY SENIOR MEDICAL REGISTRAR

VICTOR PARSONS
B M Oxon , M R.C.P
MEDICAL REGISTRAR

JOHN R RAWSTRON
M B Lond
LECTURER IN PATHOLOGY

From the Departments of Medicine and Bacteriology, King's College Hospital, London, S E 5

PARENTERAL administration of foreign serum stimulates the formation of precipitating antibodies and may sensitise the recipient, so that a subsequent dose of serum produces anaphylactic reactions Glenny and Hopkins (1922) showed that in laboratory animals a second dose of foreign serum disappears from the blood much more rapidly, and that, if this serum contains antibodies, these remain in the circulation for a very much shorter time The duration of passive immunity conferred by antitetanus serum is believed to be likewise reduced in patients who have previously received tetanus antitoxin (Payling Wright 1958)

We report here a case in which hypersensitivity to horse serum developed as the result of antitoxin therapy Circulating tetanus antitoxin and antibodies to horse serum were estimated The rapid fall in circulating antitoxin and the rise in titre of antibodies to antitoxin support Payling Wright's view

Case-record

A leatherworker, aged 20, sustained a compound fracture of the right tibia and fibula in a motor-cycle accident on Dec 5, 1958 He was given 1500 units of antitetanus serum intramuscularly, and was admitted to King's College Hospital under the care of Mr R C F Catterall A few hours later the compound fracture was explored, a skin graft applied, and the limb externally fixed 1 million units of crystalline penicillin was given intramuscularly every twelve hours for four weeks, during which time further skin grafts were applied The area of the wound was subsequently reduced to about 1 sq cm over the tibia anteriorly The patient was discharged from hospital in an above-knee plaster on Feb 25, 1959 On June 2, 1959, discharge from the wound was very slight and the patient was bearing weight on his leg without pain

On June 16, 1959, he noticed that his back was stiff and he had difficulty in moving his jaw Two days later spasms had spread to his back and abdominal muscles Tetanus was diagnosed, and he was admitted to hospital under the care of the late Dr A Gilpin

Treatment

Because of the patient's previous serum injections, test doses of antitetanus serum were given subcutaneously 0 2 ml (1000 units) and, after an interval of forty-five minutes, 1 ml (5000 units) No systemic reactions were observed, but both doses gave rise to local erythema 2 cm in diameter He was therefore given 100 mg of chlorpromazine intramuscularly, and a further 10 ml of antiserum was injected very slowly intravenously After 6 ml had been injected, he became breathless and complained of pricking in the face Tetanic spasm involved the back and limbs 3 ml of a 1 in 1000 solution of adrenaline was given intramuscularly and subcutaneously over the next five minutes He became shocked, and his blood-pressure fell to 60/0 mm Hg Because of the severe reaction, and the likelihood that the condition was chronic tetanus, no further antitetanus serum was given The patient's condition deteriorated over the next few days, spasms occurred at irregular intervals Chlorpromazine and pethidine were given for sedation and to alleviate the pain of the sustained muscular contraction A wound-swab grew *Clostridium tetani* The wound was thoroughly cleansed, extensive debridement was not attempted as this would have necessitated amputation By June 28, 1959, two weeks after his first symptoms, the patient's condition had begun to improve, the stiffness eased, and a month later he was discharged from hospital after receiving the first dose of a full course of tetanus toxoid without ill effect

Investigations and Discussion

Serum was taken from the patient on the sixth, ninth, and fourteenth days and six months after the last injection of antiserum, and its tetanus-antitoxin content was titrated in mice by the method of Glenny and Stevens (1938) The normal antitoxin values to be expected after an injection of 30,000 units of antitoxin have been estimated from data given by Barr and Sachs (1955) These values are compared with the patient's in table I The level in the patient on the sixth day is half of that expected, and all effective immunity has disappeared by the ninth day This destruction is not quite as rapid as that in animals (Glenny and Hopkins 1922), in which by the fourth day no antitoxin was detectable

TABLE I—OBSERVED AND EXPECTED SERUM ANTITOXIN LEVELS AFTER INJECTION OF 30,000 I U

Days after injection	Observed values (antitoxin units per ml)	Expected values (antitoxin units per ml)
6	1 2	2 4
9	<0 01	1 6
14	<0 01	1 0

Antibody to horse serum and to equine tetanus-antitoxin globulins was titrated by an agar-gel precipitation method, and by hæmagglutination of sensitised tanned cells The results (table II) show that the sera taken on the ninth and fourteenth days, which contained negligible amounts of antitoxin, have high titres of antibody to horse-serum proteins These antibodies were still detectable after six months

Serum taken on the fourteenth day was also tested against normal sheep, pig, and goat serum, as it has been suggested that antitoxin prepared in other animals might be used for patients sensitive to horse serum

TABLE II—TITRATION OF ANTIBODY TO HORSE SERUM AND TO TETANUS ANTITOXIN

Days after injection	Titration method			
	Agar gel precipitation		Hæmagglutination	
	Normal horse serum	Tetanus antitoxin*	Horse serum	Tetanus antitoxin*
6	1/8	1/8	1/25	1/25
9	1/128	1/128	1/625	1/625
14	1/128	1/128	1/625	1 625
180	0	0	1/25	1/5

* Wellcome brand, consisting of *enzyme refined horse globulins*, was used

Sera from all three species gave positive precipitation reactions with the patient's undiluted serum and hæmagglutination to a titre of 1/25 Though these reactions were very much weaker than those found with horse serum, the cross-reactions suggest that foreign serum should be administered with care to patients sensitive to horse serum

Summary and Conclusions

Tetanus developed in a patient who was hypersensitive to horse serum

Tetanus antitoxin in the patient's serum was estimated shortly after a dose of 36,000 units of antitetanus serum Six days later 1 2 units per ml (half the expected value) was found, and on the fourteenth day no antitoxin was detectable Precipitating antibodies to horse-serum globulins were found at a higher titre in the fourteenth-day than in the sixth-day sample and were still present, though at low titre, six months later

This case illustrates the following points

1 The *protection given by tetanus antitoxin is greatly* reduced in patients with anaphylactic reactions and may also be reduced in those who, though not obviously hypersensitive, have received horse serum before

2 Because of cross-reactions, tetanus antitoxin from animals other than the horse is unlikely to be of practical use in the treatment of those hypersensitive to horse serum

3 The most effective means of reducing the incidence of hypersensitivity reactions and their sequelæ is active immunisation, particularly of those who have received prophylactic antiserum Indeed, if this patient had been actively immunised soon after the accident he might possibly not have had tetanus

We wish to acknowledge our indebtedness to Mr R C F Catterall and the late Dr A Gilpin for permission to publish, to Miss M Barr, of the Wellcome Research Laboratories, for the estimations of antitoxin, to Dr Leslie Cole for advice on treatment of the patient, *and to Sister O Bonner and her staff for their expert nursing*

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"   a cry was soon echoing from committee to committee 'The smaller the school the better the school' (a fore runner perhaps to one of Parkinson s Laws) Now, it must be obvious to everyone that large classes are bad, but is the reverse true? Are small classes necessarily good? The answer is, no Once the numbers drop below a certain critical point they are definitely bad Every clinical teacher knows that the success of ward-round teaching depends on the presence of a *group* of students A worth-while discussion then ensues, one man is set against another, diverse opinions are expressed, and *slowly the* essential facts and truths are cleared of their irrelevancies How different and dreary are ward rounds with one solitary student! And how *little real teaching* does he get! —Prof J CHASSAR MOIR The Future of the Clinical School at Oxford a Symposium *Oxford Medical School Gazette*, 1960, 12, 95

Reviews of Books

Calcium Metabolism and the Bone

PAUL FOURMAN, M D , D SC , F R C P , senior lecturer in medicine, Welsh National School of Medicine Oxford Blackwell Scientific Publications 1960 Pp 325 37*s* 6*d*

CALCIUM metabolism has been attracting more and more attention since the appearance of a celebrated American monograph in 1948 Recent international meetings have revealed worldwide interest in such matters as the problem of fractures in the elderly, the early diagnosis of primary hyperparathyroidism, the biological half-life of bone-seeking isotopes, and the nutritional requirements for calcium and vitamin D All clinicians and other interested workers have, however, been aware of the need for an additional textbook Dr Fourman's distinguished work is therefore very welcome, and it deserves to be widely read He reviews the whole subject in matter-of-fact manner, steering a fair course between dogmatism and excessive caution 74 pages of references testify to his hard work and well-selected reading and will be invaluable to many workers in all branches of calcium metabolism Students and general clinicians, on the other hand, will be more impressed by the conciseness of the writing and the skilful balance which has been preserved between biochemical and clinical aspects There are very few illustrations, but that has kept down the cost, and the book can certainly be recommended as very good value for money

Epilepsy and Related Disorders

W G LENNOX, M D , SC D , associate professor of neurology emeritus, Harvard University School of Medicine, M A LENNOX, M D , member, Institute of Neurophysiology, Copenhagen London J & A Churchill 1960 Pp 574 (vol I) 594 (vol II) 96*s*

Dr W G Lennox spent a busy life studying the problems of epilepsy, and he acquired a vast experience of the many variations of the disease Written in conjunction with his daughter, this two-volume work brings together this knowledge and represents the clinical practice of a devoted doctor who was an enthusiastic pioneer for the welfare of epileptics He was eager to accept all the help science could give and he himself contributed both to detailed scientific applications in diagnosis and treatment and to the diffusion of a more rational and scientific attitude to the subject But he was also willing to be moved by the human problems of epilepsy, and this lent energy and enthusiasm to his endeavours especially in therapy and management For many years, as head of the seizure division of the Boston Children's Centre, he guided the approach in this subject both of this hospital and of American pædiatrics in general All this is woven into the book, which presents the modern view of epilepsy for which Lennox was largely responsible

The first volume is concerned mainly with clinical description, the second rather more with detailed diagnosis and treatment the last chapter of the first volume, on genetics and the broad factors of causation, bridges the gap A useful list of references both to books and papers on the subject is appended

Although this is a full and comprehensive account of epilepsy and will be an essential source of reference to neurologists for many years to come, it remains in style and emphasis the personal testament of a doctor no bad thing perhaps at a time when science often seems temporarily to be in competition rather than collaboration with humanism in medicine

Chemicals in Food and in Farm Produce Their Harmful Effects

FRANKLIN BICKNELL, D M , consulting physician to the French Hospital, London London Faber & Faber 1960 Pp 180 12*s* 6*d*

THE many substances now being added to our food have become a nightmare to legislators and to other people who have thought about this subject during the past fifteen years, and this book gives an interesting account of some of the additions The first chapter (on naturally occurring poisons) and the last (on the dangers of insecticides and similar substances to worms, fish, and insects) are perhaps the best The author is a firm believer that food, the whole food, and nothing but the food, is the only safe and proper thing to eat Flour must be unbleached, fats not hydrogenated, colouring-matter and emulsifying agents strongly discouraged So far so good, but here and there he has overstated his case How true is it, for instance, that toxic substances added to our food explain many of our recognised congenital abnormalities? Fluoride is one of the few additions to food which Dr Bicknell judges worthy of consideration

There are advantages as well as disadvantages in processing foods for a civilised community, and many people think that our scientists, industrialists, and legislators have not done all that badly by most of our foods—so far at any rate

This is a good and well-documented book It can be recommended to objective readers who are not likely to be frightened by the possibility of finding " death in the pot "

The Collected Papers of Paul Ehrlich

Compiled and edited by F HIMMELWEIT, M D , PH D , F R C P E , director, department of virus research, Wright-Fleming Institute, St Mary s Hospital Medical School, London With the assistance of the late MARTHA MARGUARDT London Pergamon Press 1960 Vol 2 Pp 562 Vol 3 Pp 615 £8 each

THERE were three main phases in Ehrlich's career, and if his published works be arranged according to their subject they are found to be in approximately chronological order His graduation thesis was upon staining methods using the aniline dyes which had become available for the first time a few years before, and these same dyes, used as chemical reagents, occupied him until 1891 Then the discovery of antitoxins by von Behring and Kitasato turned his attention to immunology (and later to the immune phenomena provoked by certain transplantable tumours) By 1904 techniques had been described, notably by Laveran and Mesnil, for the maintenance of strains of some parasites in laboratory animals, and Ehrlich resumed his work with dyes But he was now concerned with their action in experimental trypanosomiasis and spirillosis These were the studies which led, in 1909, to salvarsan, and which continued until his death, six years later, at the age of 61

These two volumes of the series cover the second and third of these periods One contains just over fifty articles on immunotherapy and immune reactions, and it includes the classic monograph on the assay of diphtheria antitoxin which was written in the establishment created by the State for Ehrlich to head, the Royal Prussian Institute for Serum-testing (housed partly in a stable, partly in a converted bakery) The other volume has a similar number of papers on chemotherapy, beginning with his first venture, when he demonstrated the action of methylene-blue in malaria Ehrlich was the son of a Silesian innkeeper, and the article concludes with a delightful, but almost irrelevant, note upon a little known physiological property of newly brewed beer

These books are beautifully bound and printed, because the original text has been used throughout, most of the contents are in German Translations are appended, however, to some of the most famous papers

Equipment for the Disabled

Compiled by MARGARET AGERHOLM, M B , lecturer, ELIZABETH M HOLLINGS, M A O T , head occupational therapist, WANDA M WILLIAMS, M A O T , warden, Mary Marlborough Lodge, Nuffield Orthopædic Centre, Oxford London National Fund for Research into Poliomyelitis and Other Crippling Diseases 1960 4 vols 120*s*

MANY patients and many institutions have developed special skills and devices to cope with almost every aspect of an incapacity Unfortunately there is no clearing-house for collating information on their methods, or for making it available to a wider circle The council of the Poliomyelitis Research Fund have gone a long way towards remedying this by publishing this " index "

Each volume is a stout folder, containing a number of loose-leaves in an "open-flat" type of steel clip These pages are indexed under such headings as Transport, Cooking, and Personal Toilet Each item has a separate page, with an illustration and an address from which it is obtainable The equipment is of three varieties specially manufactured, purchasable in ordinary shops, but with a particular value for the disabled (for example, an electric iron which weighs only 2 lb), and home-made (such as devices for turning keys or door-handles)

The index, sold on a non-profit basis, is to be supplemented by further pages issued to purchasers from time to time It should be available in every hospital

Urology in General Practice

IAN PARTON, M B, B SC, F R C S, assistant urologist, Auckland Hospital, New Zealand London Butterworths 1960 Pp 293 45s

DESIGNED for the general practitioner as a guide to procedure in urological disease and emergency, this book abounds in good humour and common sense and gives a brief survey of current urological practice without going too far into the realms of academic controversy From it the practitioner will gain a shrewd idea of the significant combinations of symptoms and signs in genitourinary disorders, and the indications for seeking specialist advice This advice may vary according to the available means for diagnosis and treatment, and also the inclination and ability of the practitioner to perform minor surgery Conditions in New Zealand clearly differ from those in urban areas of Britain access to a urological centre may be more difficult so that there is greater scope for the practitioner to make diagnostic decisions and to undertake emergency treatment Nevertheless the practical information in this little book will be of interest to all as a thoroughly sensible review

Disc Lesions and Other Intervertebral Derangements

E J CRISP, M D, D PHYS MED, consultant physician emeritus in physical medicine, Guy's Hospital, London Edinburgh E & S Livingstone 1960 Pp 158 15s

IT is a Shavian parodox that doctors write most on those diseases about which they know least Certainly the number of books and articles they continue to produce on such topics as spinal arthritis, postural defects, and disc protrusions indicates the problem posed by the multitude of patients seeking relief from backache and sciatica

Dr Crisp makes no claim to have solved this problem His book is not prefaced (as many are) with a lengthy and hypothetical discussion on the ætiology of backache He is concerned only with the practical management of some half-dozen clearly defined syndromes associated with pain in the back Manipulation and traction, the mainstays of his method, are described in detail, but manipulation is not extolled as a universal panacea, and traction is not applied, Procrustean fashion, to every patient An interesting use is made of strapping, to relieve the discomfort of an acute disc prolapse, and he attributes the beneficial effects of the old-fashioned belladonna plaster, not to its medicinal properties, but to the skin tension and restriction of movement it produced

In recent years the treatment of back pain has become increasingly conservative, and this is a very useful primer on nonoperative measures From later editions one would like to learn the author's views on the place—if any—of sedatives, relaxants, and other drugs

Disease and the Advancement of Basic Science

Editor HENRY K BEECHER Cambridge, Mass Harvard University Press London Oxford University Press 1960 Pp 416 100s

WHAT is the best understood of all diseases? It is disconcerting to learn of Dr Alex Bearn, of the Rockefeller Institute, that it is one of which many doctors know little Yet, as he points out, sickle-cell anæmia and the related hæmoglobinæmias are the only diseases of which we can be said to have a ' molecular knowledge" (The abnormality is an inherited anomaly of the hæmoglobin molecule in the reduced form the molecules cohere, to produce needle-like crystals which are longer than the diameter of the red cells, and so deform them) The chemical and physical data yielded by the investigation of such diseases are important contributions to non-clinical sciences The same is true of the endocrine disorders, which are commonly the first diseases a medical student studies He sees in them a demonstration of the part physiology has played in the advancement of medicine yet they are, in fact, outstanding examples of a converse relationship by which the study of a pathological process has cast light upon normal function

This symposium is concerned with just this relationship of medicine to the ancillary sciences Only three of its twenty-one chapters, however, deal with hæmatology and the ductless glands The others examine the results of research into (among other conditions) virus infections, rheumatism, and deafness All are written in masterly fashion by acknowledged experts, but that by Dr Percival Bailey is particularly fascinating, for he reviews the steps by which our understanding of neurophysiology has advanced These come from observations as far apart as those of Hippocrates when a psychotic patient developed malaria, and of Hoffmann when he was accidentally poisoned with lysergic acid

Medical Electronics (*Proceedings of the Second International Conference on Medical Electronics, Paris, 1959* London Iliffe 1960 Pp 614 £7 5s)—Edited by Dr C N Smyth, this book records a conference that attempted "to unite the disciplines of medicine and electrical engineering" 80 papers are given in full, with the subsequent discussions, and some 60 others in abstract Most of the papers are in English but some are in French Many of the abstracts are rather too short, and some of the papers are on subjects little connected with electronics, though interesting in themselves There remain many able contributions describing the design, construction, and application of scientific instruments for the collection of physiological data in human or animal subjects A useful introductory section on electrophysiological techniques includes excellent papers on muscle potential amplifiers (L H Montgomery and Sam E Stephenson) and on eye-movement recording (by several British authors) The book should find a place in every medical library, for it contains an abundance of practical information not conveniently available elsewhere Regrettably, much of the enterprise and ingenuity revealed here will never be fully exploited Clinicians generally prefer less spectacular methods of investigation, and on the whole they are right What is needed is for first-class physicists and electrical engineers to join teams of doctors in basic research, resisting the temptation to dissipate energy in producing more instruments or gadgets The International Federation for Medical Electronics would do well to organise smaller meetings for the study of more fundamental problems at a higher intellectual level Further gatherings of back-room boys may be useful but will not be decisive

The Electrical Activity of the Nervous System (2nd ed London Pitman Medical Publishing Co 1960 Pp 273 35s)—The new edition of Dr Mary Brazier's book remains a valuable source of reference to classical work on the electrical activity of the nervous system For the neurologist it outlines clearly and succinctly the electrophysiological background of clinical phenomena in the nervous system Although clinical practice must always have a discipline and frame of reference of its own, it must also take cognisance of established physiological facts, and neurology is entering once more a phase in which clinical problems in nerve and muscle function must be increasingly interpreted in terms of disordered physiology Dr Brazier's book is a useful guide to established fact and worthwhile hypothesis It also fulfils another and increasingly important function in bridging the gap between the findings of experimental and laboratory neurophysiology and those of clinical experience It can be recommended as an up-to-date and balanced guide both for the final-year physiology student and the clinician who wishes to begin or renew his acquaintance with the electrical activity of the nervous system

THE LANCET

LONDON 3 DECEMBER 1960

Myocardial Infarction

The natural history of coronary occlusion and myocardial infarction has become even more important now that anticoagulant drugs have been accepted as standard treatment in the acute phase and are commonly used in the long-term prophylaxis of further attacks Two studies have largely confirmed earlier reports about the prognostic factors influencing the outcome of the acute attack, and illustrate how selection of cases affects the mortality-rate Beard et al [1] studied 503 U S veterans, all suffering from an initial myocardial infarction confirmed by an electrocardiogram Since these workers were particularly interested in the younger age-groups all records of those under 50 years were included, but only a sample of available patients over that age were studied, thus 36% of patients were under 50, and the mortality in the first two months for the whole series was 15% By contrast White et al [2] found a mortality in the first six weeks of 61% among 344 unselected male patients, of whom 70% were over 60 years of age and 28% had had a previous infarction In both series the mortality rose considerably with advancing age—in the series of Beard et al, in those over 60 the mortality was more than double that in those under 60 Plainly the different age-distribution accounts for much of the disparity between the two series and Beard et al's series is also likely to have contained a lower proportion of patients who died shortly after admission In both groups severe shock or congestive failure more than trebled the immediate mortality, and White et al found that shock was a particularly bad sign in patients with a previous infarct High fever for more than a few days, a leucocytosis above 15,000 per c mm, and any cardiac arrhythmia were all associated with a higher immediate mortality Beard et al report a mortality of more than twice the overall rate in cases where thromboembolic complications developed, but do not state whether death was usually due to pulmonary embolism In both series hypertensive patients had a higher mortality in the acute attack, Beard et al found a significantly worse prognosis in patients with angina for longer than a month before infarction, while White et al were particularly impressed by the high mortality in young diabetics Generally speaking, bad prognostic signs are those indicating a large area of infarction

Whereas the immediate mortality-rates vary widely, the five-year-survival figures, as Beard et al point out, agree remarkably closely This is emphasised by McMichael and Parry [3] in a critical analysis of the factors influencing the long-term prognosis after coronary-artery occlusion Their review of the numerous published series [1, 4–18] suggests that about 65% of survivors of the acute attack will be alive after five years, but the prospect declines with increasing age, so that those series [11, 16] containing a higher proportion of old patients have a correspondingly diminished five-year-survival rate Certain features of the acute illness not only worsen the immediate prognosis but also militate against long-term survival Especially notable among these are congestive failure, cardiac enlargement, arrhythmias, previous infarction, and diabetes chances of survival for five years are roughly halved in those with cardiac failure [9, 12–15] Other factors, such as economic class and ability to take extra care of the health, may contribute to a survival-rate above the average McMichael and Parry therefore conclude that the slightest degree of unintentional bias in the selection of patients for long-term anticoagulant treatment and control groups could profoundly influence the results, particularly if the numbers are small They suggest that such bias may in fact have vitiated results, since in three large trials [19–21] the survival-rates of the control groups were rather below the lower limit expected in a group of untreated patients, whilst in another trial [22] heart-failure was twice as common in the control group as in the treated group Furthermore, no treated group has yet had a survival-rate above the upper limit of the range expected in untreated cases—though admittedly most results are slightly better than the average

McMichael and Parry suggest that the only benefit apparent from long-term administration of anticoagulants in the two most careful studies yet reported—those of Bjerkelund [20] and the Medical Research Council [23]—is a slightly lower mortality-rate in the first few months after infarction Bjerkelund found this only in men under 60, and the difference was also less notable in older men in the Medical Research Council trial In neither series did women benefit at all Reported trials have invariably stressed the reduced incidence of recurrent infarction in treated patients, but recurrent infarction is often difficult to diagnose, and sudden death after previous infarction is not always due to this cause In any series where sudden death from other causes is not clearly excluded, the incidence of recurrent infarction is liable to be overestimated, and this criticism may apply to the M R C trial In addition there is disagreement as to the duration of protection BJERKELUND found no difference in his two groups after one year nor at any time among those over 60, whereas the M R C trial suggests that protection continues into the second year

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[1] Beard O W Hipp H. R. Robins M Taylor J S, Ebert R. V, Beran L G *Amer J Med* 1960 28 871

[2] White A E., Moore F J, Marmorston J *Arch intern Med* 1960, 105 859

[3] McMichael J, Parry E H O *Lancet*, Nov 5 1960 p 991

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[6] Smith C *J Amer med Ass* 1953, 151 167

[7] Cole D R Singian E B, Katz, L N *Circulation* 1954 9, 321

[8] Weiss M M *Amer J med Sci* 1956 231 9

[9] Helander S Levander M *Acta med scand* 1959 163 289

[10] Juergens J L, Edwards J E, Achor, R W P, Burchell, H B *Arch intern Med* 1960 105 444

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[13] Honey G E Truelove S C *Lancet* 1957 i, 1209

[14] Bjork, G, Sievers J Blomquist, G *Acta med scand* 1958, 162 81

[15] Block W J Crumpacker E L Dry T J Gage R P *J Amer med Ass* 1952 150 259

[16] Westlund K Hougen A *Acta med scand* 1956 154 suppl 315

[17] Olsen O C, Kahrs, T, Rømcke O, Lingjærde P *ibid* 1956 156 suppl 319

[18] Richards D W Bland E. F White P D *J chron Dis* 1956 4 415

[19] Nichol E S Keyes I N, Borg J F Coogan T J Boehrer T J, Mullins W L Scott T Page R Griffith, G C, Massie, E *Amer Heart J* 1958, 55 142

[20] Bjerkelund C J *Acta med scand* 1957, 158 suppl 330

[21] Suzman M M Personal communication to McMichael and Parry (footnote 3)

[22] Manchester, B *Arch intern Med* 1957, 100 959

[23] Report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council *Brit med J* 1959, i 83

MCMICHAEL and PARRY's analysis has made them critical of the claims advanced for long-term anticoagulant therapy, particularly as a means of prolonging survival or preventing recurrence FLOREY[24] has remarked that the assumption that an anticoagulant will prevent thrombus formation is not necessarily correct cardiac infarction has been reported in hæmophiliacs[25,26] and GILCHRIST and TULLOCH[27] found no real difference between the incidence of mural thrombi in patients who were receiving anticoagulants and those who were not If anticoagulant drugs prevent arterial thrombosis, why should their prophylactic action apparently be confined to the first few months after infarction? MCMICHAEL and PARRY suggest that either their effect may be in some way related to the healing phase of infarction, or sudden cessation of treatment in controls renders them unduly prone to further infarction

The acid tests of any form of treatment are whether it is effective and whether it is safe MCMICHAEL and PARRY are clearly unconvinced, and they remark that fatal hæmorrhage can result from the use of anticoagulants If their arguments are accepted—and correspondence has already shown that their reservations are shared by others—then our earlier estimation of long-term anticoagulant treatment[28] was overhopeful and it would seem logical to discontinue anticoagulant therapy after six months or a year, as BJERKELUND originally recommended

The Biology of Metastasis

AMONG the more perplexing current biological problems are those concerned with cell "recognition" and cell differentiation Up to what level can cells, as distinct from the whole animal, discriminate between "self" and "not self"? Have cells the inherent mechanisms to develop into organs and tissues, without outside "information"?

In 1908 WILSON[29] noted that when sponges were squeezed through a fine silk mesh, individual sponge cells were liberated Left in a dish of sea-water, the individual cells moved over the surface of the dish, came into fresh contact with each other, and reaggregated to form new sponges HOLTFRETER[30] found that amphibian embryos could be dissociated into single cells by briefly raising the pH of their environment to about 9 7 This treatment did not interfere with the viability of the isolated cells or with their subsequent differentiation, when their environment was brought back to physiological pH8 When mixtures of different types of cells, dispersed from the same embryo, were cultured, it was clear that, although initially any of the cells might unite indiscriminately with any other cells, they eventually sorted themselves out so that aggregates of like cells were formed HOLTFRETER concluded that the sorting-out processes were largely due to positive or negative affinities of the cells that is to say, in the reaggregation process cells of the same tissue (homotypic) making contact with each other would cohere permanently, whereas cells from unlike tissues (heterotypic) would not

In 1952 MOSCONA[31] described the reaggregation of cells from chick embryonic organs which had been dispersed by the action of trypsin He found that aggregates formed in suspensions of chondrogenic cells gave rise to nodules of cartilage, suspensions of isolated mesonephric cells produced aggregates which developed into vesicular and tubular structures resembling the excretory tissue of the embryo Later MOSCONA showed that, when suspensions of chondrogenic and myogenic cells were cultured together, aggregates were formed in which the cells sorted themselves out so that an inner nodule of cartilage was differentiated, and this was surrounded by an envelope of myogenic cells In 1957 MOSCONA[32] described tissue specificity in the reaggregation patterns of trypsin-dispersed chondrogenic, nephrogenic, and hepatogenic cells from the embryonic mouse Cells from like organs aggregated together Furthermore, when mixed cell-suspensions from 12-day-mouse and 4-day-chick embryos were cultured, chimæric (organ) aggregates were formed provided that the cells from the two species came from the same type of tissue Cells from different tissues, even when obtained from the same embryo, did not form stable heterotypic aggregates In this type of experiment, therefore, tissue-specificity took precedence over species-specificity Lately P WEISS and A C TAYLOR[33] have shown that organs from 8–14-day-old chick embryos, which have been disaggregated with mixtures of trypsin and papain, re-form and undergo a remarkable degree of development when cultured on the chorioallantoic membranes of 8-day-old embryos After 9 days' culture on chorioallantoic membranes, grafts of completely disorganised metanephric cells form symmetrical organs with clearly defined cortices, medullæ, tubules, and malpighian corpuscles

The experimental evidence shows that, in the sorting-out processes that occur in cell suspensions, the capabilities of cells for differentiation and specialised recombination are associated with information on the cell surface which makes recognition at cell level possible L WEISS[34] has suggested that this recognition may be expressed in terms of cell adhesion TYLER,[35,36] P WEISS,[37,38] and SPIEGEL[39] suggested that cellular adhesion invokes mechanisms similar to antigen-antibody reactions, and that differences in cell adhesiveness may reflect antigenic change It is therefore interesting that WEILER[40, 41] has demonstrated antigenic differences between normal rat liver cells and those from butter-yellow hepatomas It might be expected that there would be different contact reactions between normal cells on the one hand, and between normal and malignant cells on the other

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[24] Florey H *Ibid* 1960, ii 1329
[25] Borchgrevink C F *Lancet* 1959 i 1229
[26] Stewart J W Acheson E D *Ibid* 1957 i 1121
[27] Gilchrist A R Tulloch J A *Scot med J* 1956 1, 1
[28] *Lancet* 1958 i 417
[29] Wilson H V *J exp Zool* 1908 5 245
[30] See Townes P L, Holtfreter, J *Ibid* 1955 128 53
[31] Moscona A *Exp Cell Res* 1952 3 535
[32] Moscona A *Proc nat Acad Sci*, *Wash* 1957, 43 184
[33] Weiss P, Taylor, A C *Ibid* 1960 46 1177
[34] Weiss L *Int Rev Cytol* 1960 9 187
[35] Tyler A *Proc nat Acad Sci* *Wash* 1940 26 249
[36] Tyler A *Ibid* 1946 32, 195
[37] Weiss P *Growth* 1941 5 suppl p 163
[38] Weiss P *Quart Rev Biol* 1950 25 177
[39] Spiegel M *Biol Bull* 1954 107 149

The work of ABERCROMBIE et al[42] has revealed that when sheets of normal embryonic fibroblasts in culture come into contact with each other, either the cells move away from each other or, if this is not possible, migratory movements stop altogether, this feature has been termed " contact inhibition " On the other hand, when various types of malignant cells come into contact with normal fibroblasts under the same experimental conditions, the malignant cells move through and over sheets of the normal cells As ABERCROMBIE et al[42] pointed out, it would be rash to directly relate in-vitro experiments with embryonic tissue to the observed invasive behaviour of human tumours in vivo Nevertheless, invasion of normal tissues by malignant cells may be related to surface changes that make the malignant cells less adherent to themselves and other cells, and thus more mobile than normal cells Moreover, COMAN's work[43, 44] suggests that the constituent cells of some tumours are less sticky for each other than the constituent cells of normal organs If the observations of ABERCROMBIE and COMAN apply generally, then invasion and metastasis can be regarded as deficiencies in the adhesiveness of tumour cells Thus the problem is defined rather than explained, since pathetically little is known about the biophysical bases of adhesion

When the reasons for lack of adhesion are sought, three main factors must be considered These are the tumour-cell surface, the surface to which it sticks, and the microenvironment at the cell surface The study of each of these three factors is extremely difficult It is not agreed what constitutes the cell surface, since extraneous materials may or may not be regarded as an integral part of the cell On electronmicrographic evidence it seems likely that the plasma membranes of adherent cells are invariably separated by about 200Å, thus in a sense cells can be regarded as sticking to intercellular or intermembranous material Is this material the key to invasion and metastasis ? The microenvironment at cell surfaces is probably quite different from the enveloping tissue-fluids, owing to physicochemical influences, and may vary at different parts of the cell surface owing to microheterogeneities All or any one of these factors could bring about changes in adhesive potential

As more knowledge is obtained about factors affecting cell surfaces and contact, it may conceivably become possible to influence these therapeutically In this event, it might prove feasible to control invasion and metastasis of malignant disease, leaving the field open for safe surgical removal of primary growths

Hospital Infection

AT the end of October WILLIAMS, BLOWERS, GARROD, and SHOOTER[1] produced a book of great importance on hospital infection No better single source of information on this subject is to be found anywhere, and a corresponding welcome is assured It is because of this, and because of the excellence and authority of the work, that we look at its contents with special care Of the three challenges it offers, the first is the challenge of the knowledge that our hospitals are doing harm to some of the sick within their walls The second and third are put by the authors in their preface

> " We anticipate criticism of the text on two grounds It may be said that too much space is devoted to staphylococcal infection, perhaps because the authors have themselves made a special study of it Secondly, we may be accused of too agnostic an attitude because we have expressed firm conclusions only when the evidence seems fully to justify them "

To examine these challenges separately may be as good an approach as any to the task of describing and commenting on a book which deserves and requires to be read by clinicians, matrons, nurses, administrators, laboratory workers, and general practitioners

First, the challenge of the subject itself Some deprecate reiteration of appeals[2] because, by a few simple and obviously necessary steps, they have reduced the infection-rate in clean surgical wounds to a very low level, and it is encouraging to know that this can be done Simply for a surgical chief to say to all the members of his unit that wound sepsis is a most important problem which he wishes to be fully and frankly assessed, discussed, and unemotionally dealt with will of itself often work a transformation If action includes the recording of all infections and (still better) the ascertainment week by week of the infection-rate and its discussion by the unit, there is sure to be great improvement But (leaving aside occasional and probably inevitable episodes of epidemic spread) can surgical units reduce clinical infection to about 1–2% of clean surgical wounds, without distorting surgical and nursing practice in any way ? If they could, this would be a great advance on the present state of affairs when sepsis-rates of around 10% are not at all unusual Professor WILLIAMS and his colleagues estimate that, on the average, surgical wound sepsis keeps the patient in hospital about a week longer than is necessary, and they say that, if their conclusions are applicable to the $1^1/_2$ million operations performed in Britain each year, the annual cost is that of 1 million extra patient-days in hospital Since this is the conclusion of an exceedingly cautious and conservative approach to the figures and possibilities, it must make us all profoundly hope and pray that the infection risks inherent in all hospitals are being fully taken into account in

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[40] Weiler, E *Z Naturf* 1952 7, 324
[41] Weiler, E *ibid* 1956 11B, 31
[42] Abercrombie M , Heaysman J E. M , Karthauser, H M *Exp Cell Res* 1957, 13 276
[43] Coman, D R. *Cancer Res* 1944 4 625
[44] Coman, D R. *ibid* 1953 13, 397

[1] Hospital Infection Causes and Prevention By R. E O WILLIAMS R BLOWERS L P GARROD, and R. A SHOOTER. London Lloyd-Luke (Medical Books) 1960 Pp 298 35s
[2] Flemming C. *Lancet* 1959 i, 257

planning new hospitals Some plans that have been produced for "rationalising" the allocation of operating-theatres and reducing their size may well need re-examination in the light of what infection costs Moreover, the enthusiast who crams all possible beds into his wards should take note of the simple affirmation that "the distance between bed centres should not be less than nine feet" (p 191) Further thought, too, should be given to providing isolation for general surgical and medical patients who need it—a subject admirably set forth and judicially analysed here This first challenge, therefore, is to the whole profession It is in effect to each one of us to read the book and then consider his own role Few will fail to discover ways in which they avoidably increase infection risks or neglect actions by which they could reduce dangers

The second challenge concerns the space given to staphylococcal infection—three chapters being wholly devoted to staphylococci out of ten on the epidemiology of hospital infection But, as the authors say, staphylococcal infection is the one which, in its many different forms, has caused most worry and perplexity in recent years, it is exceedingly common and sometimes fatal, the mode of transmission is still obscure, and the precautions which matter most in preventing it have yet to be certainly identified Whether the epidemiological picture will be fundamentally altered by the penicillinase-resistant penicillin introduced since the book went to press we cannot yet be sure[3] certainly the outlook for the individual infected patient is now much more favourable, but the general picture has not yet changed Moreover, the authors deal faithfully with infections due to gram-negative bacilli, diseases of the urinary and intestinal tracts, tetanus, and gas-gangrene, and others of which some have doubtless been included mainly to keep the record straight They have first-rate chapters on administrative control of hospital infection and on operating-theatre design and practice Altogether, therefore, we may well decline this second challenge, fully acquitting the authors of having given too much time and thought to staphylococci

When, however, they wonder whether they will be accused of "too agnostic an attitude", their challenge must be taken up They remark that in medicine it is easy to dogmatise and to dress up opinions in the guise of ascertained facts, and they are right to deplore such habits But in some of their writing they can be held to express opinions which call for critical comment For example, the use of water at 75°C or 100°C is more than once defended against critics who are supposed (one gathers) to advocate autoclaving because they fear that clostridial infection is often conveyed by boiled instruments, or even bedpans But the case for the general use of the instrument autoclave or the ready sterilised and assembled syringe and needle does not in fact rest on such fears The reason why boiling has been blamed is that it is often abused[4] indeed in certain parts of their text the authors show themselves well aware of these abuses When a sterile instrument or syringe is needed in a hurry—and that is not the exception—boiling is liable to be perfunctory, and what is found on culturing a poorly boiled rubber catheter is not merely sporing organisms but staphylococci and coliforms (Hollow tubes of all kinds are more difficult to clean and to sterilise than most nurses and doctors seem to realise) The authors show in chapter XVIII that they know how a hospital can benefit from central sterile supply and reliable autoclaving Why then do they go so far out of their way to make points about the efficacy of adequate boiling which are well known to all but which still do not make the method advisable for hospital theatres and wards or inoculation clinics? However valuable boiling may be to the bacteriologist in his own laboratory, especially where he is his own technician, we cannot think it wise to appear to press for a method which, in the conditions actually prevailing in practice and in most hospitals, is wide open to abuse Moreover, before the medical profession raises the bogy of costs of new procedures, it ought to ascertain the true price of all the wasted time, labour, destroyed decorations, and avoidable cross-infection that may be attributed to some of the mock-sterilisation rituals now being used It should also discover whether an educated public opinion is in fact unwilling to pay the price for a real guarantee of sterility Enough evidence of failure to sterilise is quoted by Professor WILLIAMS and his colleagues to trouble most doctors' consciences, and many of the residual problems of hospital infection may well be found to be psychological rather than technical Surely we can agree on one simple rule articles accepted as sterile must carry a valid guarantee of having been through an effective process of sterilisation

Two other points for criticism—again probably the outcome of agnosticism—need to be mentioned

Firstly, on p 141 the spread of serum hepatitis (other than by transfusion) is said to be completely preventable by the simple rule that no needle that penetrates the skin of one patient is used for a second without being sterilised This might fail to convey to some that any syringe attached to the needle will also have to be sterilised

Secondly, on p 168 the question whether refrigerated ventilation is necessary for operating-theatres in Britain is answered in the negative because in London the daytime maximum temperature exceeds 77°F on an average on only twelve days of each year and in Glasgow on only three days Since the immediately preceding text correctly states that most British surgeons like an air temperature of 65–70°F, and since operating-theatres must contain a great many irremovable heat sources such as the patient, members of the staff, and lights, this dismissal of a difficult problem may well be found inadequate if the object is to provide tolerable conditions throughout an operating session lasting several hours

The purpose of challenges is presumably to be accepted, but we take up this one only because we think that the agnosticism of which the authors speak in their preface may have created needless contradictions in their essential message, and that these contradictions could confuse readers who earnestly wish to do what is needed to make hospitals safer places

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[3] *Brit med J* Sept 3 1960 *Lancet* Sept 10 1960

[4] Nuffield Provincial Hospitals Trust Present Sterilising Practice in Six Hospitals London 1958

Annotations

RETIREMENT OF SIR JOHN CHARLES

FROM this week we must cease to think of Sir John Charles as chief medical officer of the Ministry of Health

Son of a general practitioner in a mining town of County Durham, he was medical officer of health for Newcastle when in 1944 he was invited to join the Ministry as one of Sir Wilson Jameson's deputies In Newcastle—the city of his quietly brilliant university career—he had done much to raise standards of health, particularly in the slums, and with his friend James Spence had set on foot the now famous studies of the health and nutrition of children At the Ministry his high intelligence and manifest sincerity again won the esteem of his colleagues He showed himself a person of extraordinary patience, and to those trained in other disciplines he also conveyed something of the grandeur of medicine as a branch of learning—something of its particular tradition of intellectual integrity

> "He will be remembered," writes an associate, "not only as a learned man, with a distinction of mind which was a delight to all who had to do with him, but as a very wise one Wisdom can be imparted in many ways John Charles was at his best in unhurried discussion from behind his own desk with a perplexed colleague sunk in the depths of his official armchair The solutions he then put forward had the simplicity and inspired common sense which mark wisdom in action."

In the World Health Organisation he found other and different scope, and he was recently president of the World Health Assembly Alike in international and in national work, in public and in private affairs, his capacity for taking pains, and his constant wish to help, have been very valuable, and in earning respect he has gained also affection With his special qualities still growing, retirement from one kind of service must mean only a change to another

ON CLOSING A CRANIAL FISTULA

THE classical indications for closure of a craniopharyngeal fistula by a fascial graft were persistent cerebrospinal-fluid rhinorrhœa—an absolute indication—fissured fracture crossing the roof of a nasal sinus, anosmia, and meningitis following injury With the advent of chemotherapy and antibiotics, meningitis became increasingly curable, and this complication became so lightly regarded that some patients were allowed to suffer repeated attacks before surgical closure of the fistula was attempted [1]

Of late years reports have appeared of recurrent attacks after injury to the nasal sinuses [2] [5] or the petrous bone [6] - and operations on the nose or ear, or owing to congenital malformation In traumatic cases the injury may have been sustained a long time before [3] [8]—as long as thirty years [9]—while a history of rhinorrhœa and radiological evidence of fracture may be absent [10] [11] Both the delay in the onset of symptoms and the absence of rhinorrhœa are due to occlusion of the fracture line by a cuff of meninges with or without brain tissue [12] Such a situation is dangerous in the event of upper-respiratory infection Congenital malformations which lead to meningitis include nasal encephalocele, dermoid cyst or sinus, epidermoids, and persistent fœtal fistulæ—for example, through the petrosquamosal suture or foramen cæcum

Bøe and Huseklepp [1] emphasise again that meningitis even long after a head injury should arouse suspicion of a fistula, and that recurrent attacks, in the absence of any other cause, warrant surgical exploration They distinguish carefully between relapse and recurrence Surgical treatment is by craniotomy with application of a fibrous sheet—usually autogenous fascia lata—intradurally over the breach in the dura and the bone This treatment should be advocated clearly and firmly despite their conviction of the need for surgical treatment, Bøe and Huseklepp persuaded only 2 out of 5 patients with recurrent meningitis to submit to operation In these 2, injury to the roof of the nasal sinuses was found, this had not made its presence known in any way other than through the multiple attacks of meningitis

Of the surgical principles that have weathered the wind of antibiotic change, one is that a persistent cerebrospinal fistula should be closed

HUMAN FLOTSAM

THE National Council of Social Service has published an interesting account [13] by Mr Merfyn Turner of a common lodging-house in London Most of the 300 men housed there were fairly long-stay residents three-quarters of them stay for more than six weeks and half for more than six months, though a good number were continuously on the move About 60% were in regular work (a high proportion for such places) and perhaps 25% had recent experience of prison—though the management liked to think the number much less Some 20 men were of severely subnormal mind as a primary condition and about 12 were mentally ill—often quite grossly schizophrenic, so it seemed Otherwise the community seemed to be made up of those shiftless, unreliable people often termed "inadequate psychopaths" with no stake in anything, no identifications, and no future, though a number of old-age pensioners were in slightly different circumstances But lodging-houses tend to gather their own differing clientele

Staff of lodging-houses with a religious (like this one) or philanthropic background usually had a clearer idea what they were trying to do, but the evangelistic rehabilitation ideals of the late 19th century could scarcely be achieved in this sordid environment The superintendent and his 4 or 5 senior staff seemed to be quite able and concerned people, a group of lonely men united in their loneliness, living in very poor conditions on tiny salaries The 20 porters-cum-cleaners were on a level with the lodgers Rehabilitation, Mr Turner says, is a matter of relationships, and the superficiality of these, staff with lodger, was the most consistently disappointing feature of the life Reformative value seemed almost totally lacking, and even religious conversion—in this setting—was highly suspect The policy of ignoring a man's past, while theologically sound perhaps, prevented the staff from coming to grips with the lodgers' basic problems From lodging-house perspective, the National Assistance Board and charitable institutions seemed largely ineffective and their incentives (positive and negative) quite inadequate to make much impression on this type of man A strong case could be made for firmer handling corpus is often much too habeas, though today's prisons are not really the answer Looking to the future, Mr Turner has a few good (and, one fears, quite unattainable) ideas Among other things, he would cut down the size of the houses to about 60, split up the vast dormitories to small units, employ casework and group techniques, train and upgrade the staff, and bring in women to help

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[1] Bøe J Huseklepp H. *Amer J Med* 1960 29 465
[2] Traut, E. F *J Amer med Ass* 1945 129 273
[3] Hoyne, A. L Schultz A. *Amer J med Sci* 1947, 214, 673
[4] Galloway W H. Chambers W *Lancet* 1953 ii 68
[5] Tribuno C. W *J Pediat*, 1953 42, 609
[6] Maxwell J H *Laryngoscope*, 1953 63, 355
[7] Precechtel A. *Acta otolaryng Stockh* 1954, 44, 427
[8] Wirberg J *Nord med* 1955, 54 1288
[9] Stenger, H H *Z Hals Nas u Ohrenheilk.* 1958, 7, 65
[10] Barsky P *Canad med Ass J* 1955 72, 210
[11] Ocklitz H.-W *Mschr.Kinderheilk.* 1955, 103, 12
[12] Ectors L. *Scalpel*, 1957, 110 809
[13] Forgotten Men A Study of a Common Lodging House undertaken by the London Council of Social Service at the request of the Calouste Gulbenkian Foundation National Council of Social Service Inc (ref no 587) 1960 Pp 91 5*s*

Forgotten Men gives the impression of a very valuable piece of research that has not quite come off What could have been, as Mr Turner intended, a valid factual study, with appendices, index, and a survey of the literature, has ended up a well-written journalistic fragment, decorated with a few case-histories and personal impressions But the position of the researcher was evidently a difficult one, poised mid-way between staff and lodger, and it is easy to see that suspicion and prejudice made fact-gathering very hard indeed The booklet is a work of social reform rather than of science, and it deserves to stir the public conscience

METRONIDAZOLE IN THE TREATMENT OF TRICHOMONIASIS

METRONIDAZOLE ('Flagyl', 8823 R P) is a derivative of nitro-imidazole—namely, 1-β-hydroxyethyl-2-methyl-5-nitro-imidazole—which has been claimed to be an effective oral remedy for human genital trichomoniasis Cosar and Julou [1] found that this drug was highly active against *Trichomonas vaginalis* in vitro, and in vivo in the mouse There was little evidence of acute toxicity in mice, and no evidence of chronic toxicity when it was given by mouth to rats in amounts up to 50 mg per kg daily or to dogs in amounts up to 100 mg per kg daily for a month Successful clinical trials in men and women were reported by Durel et al [2 3] and by Sylvestre et al [4] First reports from this country were presented to the Medical Society for the Study of Venereal Diseases last May [5]

There is general agreement that in most cases of trichomonal vaginitis this drug, given by mouth, causes disappearance of the organism from the secretions within a few days and complete resolution of the vaginitis within one or two weeks This satisfactory response occurred in 88–96% of cases [6–9] In some cases the condition recurred during subsequent observation, but Rodin et al ,[6] who observed and tested 52 patients for three months after treatment, claimed ultimate success in 83% Only 4 of their 82 cases failed to respond immediately, and in 2 of these there was evidence that the tablets were not taken regularly and that the treatment was not continued for the full period, in the other 2 cases serum levels of the drug, estimated by the polarographic method, were considerably lower than in cases successfully treated Rodin et al suggested that immediate failures of treatment might be related to low concentrations of the drug in the serum, owing to failure to take the tablets, or to some deficiency of absorption, or perhaps to abnormally rapid excretion in the urine Of their 6 patients who later showed evidence of failure of treatment, in that the vaginitis returned and the organism reappeared, 5 admitted unprotected coitus and therefore the possibility of reinfection

Recurrence of vaginitis after local remedies has been the rule rather than the exception, and has been attributed to reinfection from the urinary tract [10] or to reinfection from the male partner Formerly *T vaginalis* was seldom found in the urogenital tracts of men, but in the past few years investigations based on careful search and good cultural techniques have indicated that infection of males is commoner than had been supposed Nevertheless the organism may still be hard to find in the infected male, and investigations as to incidence have yielded varied results Catterall and Nicol [11] demonstrated *T vaginalis* in all the female partners of 56 men with trichomonal urethritis, but Watt and Jennison [12] found the organism in the husbands of only 18 out of 30 women with trichomonal vaginitis Treatment applied only to the female patients, even though successful, is likely to be followed by the appearance of relapse which is really reinfection The results of treatment with metronidazole of men suffering from the disease have been reported in relatively few cases but seem remarkably good There were no failures in 13 cases treated by Durel et al ,[3] in 15 treated by Sylvestre et al ,[4] in 20 treated by Rodin et al ,[6] and in 11 treated by Nicol et al [13]

The dose of metronidazole commonly used is 200 mg by mouth three times daily for seven days, although Nicol et al ,[13] in a preliminary report, described good results after only five days' treatment No serious toxic effects have yet been described Rodin et al ,[6] who observed their patients closely, noted mild gastrointestinal disturbances in 10 out of 82 women under treatment Individual patients complained of dry mouth, of furred tongue, and of bad taste in the mouth 1 patient had an irritating scarlatiniform rash on the arms on the day that treatment ended, and this spread to the chest and back Of their 20 male patients, 1 complained of headache and depression but continued to take the tablets In none of their cases was it necessary to discontinue treatment Serial estimations of the total and differential white-blood-cell counts were done in 41 cases, mainly during the first two weeks of treatment In 3 cases the total polymorph-count fell below 1500 per c mm , which is usually accepted as the lower limit of normal, but in all 3 cases the levels had risen to well above the lower limit of normal at the next count There were no associated symptoms The drug appears to have had no ill effects on pregnant women [6 8 9 14]

The use of metronidazole in the treatment of trichomoniasis is still in the experimental stage, and it would be unwise to draw final conclusions There seems good evidence, however, that the drug is effective in the treatment of males and females, and up to the present toxic effects have been slight There appears to be no indication for local treatment in the great majority of cases There is overwhelming evidence that the disease is transmissible between the sexes, and it is essential that sexual partners should be examined and carefully tested for the presence of trichomonal and other infections Diagnosis may present difficulties in the male, and, when a strong presumption of a shared infection exists but the organism cannot be traced in the male partner, there may be a case for treating him nevertheless

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[1] Cosar, C , Julou L *Ann Inst Pasteur*, 1959, 96 238

[2] Durel, P , Roiron, V , Siboulet, A , Borel, L J *C R Soc franç Gynéc* 1959, 29, no 1, p 37

[3] Durel P , Roiron V , Siboulet A , Borel, L J *Brit J vener Dis* 1960, 36 21

[4] Sylvestre L Gallai, Z Ethier, J *Urol int* 1959, 9, 356

[5] See *Lancet*, 1960, i, 1226

[6] Rodin P , King, A J , Nicol, C S , Barrow, J *Brit J vener Dis* 1960 36 147

[7] Willcox R R *ibid* p 175

[8] Watt L, Jennison R I *Brit med J* Sept 24, 1960, p 902

[9] McFeet M , McGill, M I *ibid* p 910

[10] Whittington M J *Brit J vener Dis* 1957, 33 80

[11] Catterall, R D , Nicol, C S *Brit med J* 1960 i, 1177

[12] Watt, L , Jennison R I *Brit J vener Dis* 1960 36, 163

[13] Nicol, C S Barrow, J , Redmond, A *ibid* p 152

[14] Scott Gray, M *ibid* p 158

Metronidazole promises to be a major advance in the treatment of a common and distressing condition which has hitherto resisted control We hope that it will not be used indiscriminately and without proper investigation Trichomoniasis is often associated with other genital infections, especially gonorrhœa and non-gonococcal urethritis and cervicitis Associated conditions should be sought and treated and tests of cure applied, and sexual partners should be investigated and, if necessary, treated

OXYGEN FOR CONVULSIONS

OUTSIDE hospital most convulsions take place in circumstances where there are no means of terminating the seizure, and treatment is usually limited to preventing the patient injuring himself In the hospital ward, convulsions are often arrested by administration of potent depressant drugs It is, however, in the operating-theatre that anticonvulsant therapy is most promptly applied Most anæsthetists have seen either the so-called " late ether convulsions " or else convulsions as a toxic manifestation of local anæsthetic drugs Termination of the convulsion by means of a small intravenous dose of a barbiturate has been an accepted form of treatment since 1936,[1] and thiopentone is nowadays the drug most often used for this purpose It is at hand in the operating-theatre and can therefore be administered within a few seconds of the start of the seizure, which is usually arrested within little more time than the arm-to-brain circulation-time Not uncommonly this treatment is followed by a period of apnœa requiring artificial ventilation

Moore and Bridenbaugh [2] have reported 93 instances of convulsions in a series of 36,113 administrations of local and regional anæsthesia They regard the convulsion as indicating a toxic reaction, the most important aspect of which is the subsequent depression of respiration and circulation, and this depression will be enhanced by administration of barbiturates They recommend, therefore, that during a convulsion attention should be concentrated on the maintenance of oxygenation so that the subsequent stage of depression may be reached without hypoxia of the vital centres and without the added depressant effect of other drugs

Attractive as may be the avoidance of drug therapy during the clonic stage, adequate oxygenation may become impossible despite administration of 100% oxygen by mask. Oxygen balance is doubly disturbed, with increased consumption due to muscular activity and uptake hampered by rigidity Furthermore, previous underventilation may have already reduced the oxygen tension of the arterial blood to the point at which desaturation is evident Under these circumstances ventilation is imperative, and Moore and Bridenbaugh recommend myoneural blockade with suxamethonium The effects of this depolarising relaxant will normally pass off within a few minutes, leaving no residual impairment of respiratory or circulatory function Curare was used in a similar manner as long ago as 1946 by Greenfield [3]

It would probably be impossible to carry out in man a trial which would yield satisfactory evidence that one of these two forms of treatment is significantly better than the other It is therefore largely a matter of personal preference whether to follow the established practice of arresting convulsions with a barbiturate, or to refrain from adding further chemicals to the bloodstream and to concentrate on maintaining oxygenation Moore and Bridenbaugh claim that in their series of 93 convulsions there was no death which could be attributed to the toxic reaction to the local anæsthetic It would be interesting to know whether their method of treatment is equally effective in the much more dangerous convulsions under general anæsthesia

SETTING A WHALE TO CATCH A SPRAT

THE risk of malignant changes supervening in certain proliferative epithelial lesions is clearly established This risk can be averted by excising the whole of the proliferative area, and the problem for the pathologist who sees the precancerous changes in biopsy material (which usually represents only a part of the whole lesion) is to decide on the magnitude of the hazard

Boddington et al [1] have correlated and compared the clinical findings in 8522 gynæcological cases with the microscopical examination of 10,000 cervical smears and a lesser number of cervical biopsies (ring, multiple, or cone) or of the amputated cervix A cytological classification for the smears had first to be devised Seven grades were made in the first, any suspicion of malignancy was ruled out, the next three covered the changes of early malignancy, and the last three those of advanced malignancy Similarly eleven grades were devised for the histological examination of the biopsy specimens, the first seven indicating increasing grades of noninvasive " epithelial instability " and the last four grades of invasive carcinoma

In the 129 cases where the cytological appearances of smears and the histological findings from biopsies could be compared, it was found that most histological grades had a corresponding cytological grade but that there was so much variation that the histological grade could not be reliably deduced from smears Boddington et al suggest that cytological changes in the smears reflect biologically important cellular changes, but that smears give no clue to the invasive properties of the deeper parts of the epithelium since they can represent only the superficial layer

In the seven-year period of the investigation, 11 cases of clinically unsuspected invasive carcinoma were detected In the same period 9 adequate smears were " false negative " for cervical carcinoma, and 14 were " false positive "—i e, histological study revealed no cause for the abnormal cells In addition, 67 cases of possible precancerous cervical abnormalities (grades 1–7) were detected, most had been clinically unsuspected Invasive carcinoma was found in 3 of these cases at an interval of at least a year after the first smear, and in none did recurrence or death follow treatment In 15 cases the abnormal cells disappeared and remained absent after biopsy, indicating either spontaneous regression or complete removal of the lesion, and in 3 others more than one biopsy was needed to eliminate the abnormal cells In many more cases the course of the disease was interrupted by surgical treatment, and nothing more could be learnt from them There remained, however, a group of 10 cases in whom, for various reasons, a persisting lesion was followed for periods of from two to five years In 8

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[1] Woolmer R F Taylor, S *Lancet* 1936 i 1005

[2] Moore, D C., Bridenbaugh L. D *J Amer med Ass* 1960 174, 842

[3] Greenfield I *Anesthesiology*, 1946 7, 299

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[1] Boddington M M, Cowdell, R. H Spriggs A I *Brit J Cancer*, 1960, 14 151

of these, abnormal cells were constantly present, but their character did not change, except in 1 case where there was a sudden change to a more anaplastic-looking type of cell, biopsy or hysterectomy revealed early carcinomas in 3 In 1 patient the cell type progressed from a lower to a higher grade, and on cervical amputation a lesion of advanced preinvasive histological grade was found In the remaining case the abnormal cells persisted for a year and then disappeared

Petersen [2] recognised lesions which carried a 30–40% risk of sooner or later becoming malignant, but Boddington et al do not believe that it is possible to predict the course in any particular case They insist that in all cases of cervical epithelial instability, however this is revealed, it is of the utmost importance to discover whether an early invasive carcinoma has been missed They are convinced that cervical smears will not reveal such a condition, and recommend full histological study in every case They regard it as unjustifiable to expect any cytological warning before invasion begins They conclude that epithelial instability usually disappears without any treatment more extensive than biopsy, but that it sometimes becomes irreversible, and in this event invasive carcinoma sooner or later develops, without any cytological warning

Thus about a third of lesions classed by biopsy as precancerous can be expected to become malignant within a year or two Cervical smears may indicate that the lesion is persisting, but will not tell us when to wait or when to amputate the cervix uteri Cervical smears may reveal a few cases of cervical carcinoma but will miss an equal number or suggest the presence of carcinoma when it is not there As a research project the 10,000 smears have served their purpose As a routine procedure, examination of cervical smears, perhaps undertaken with less care and skill than in this investigation, has yet to win an established place

SMOKING AND RESPIRATORY DISEASE

THE extensive work carried out in the past decade on the association between smoking and respiratory disease has been reviewed by the Joint Tuberculosis Council of Great Britain [3] As long ago as 1955, the majority of doctors had concluded that cigarette-smoking was responsible for a high proportion of lung-cancer deaths [4], and the Council considers that the evidence is now conclusive Cigarette-smoking has also been proved greatly to aggravate chronic bronchitis, and to impair respiratory efficiency in the healthy Yet, even though for some years few intelligent laymen can have been ignorant of the sinister role of cigarette-smoking, the number of cigarettes sold continues to increase Cartwright et al found in an inquiry in Edinburgh that a large majority of both smokers and non-smokers expressed the view that smoking might affect the health of others, but only a minority of smokers considered that the habit had harmed them personally [5] The Council believes that doctors have a moral obligation to put the facts before the public, and most doctors do seem fully conscious of this responsibility Data from 85 chest hospitals and clinics indicate that in 60 of them physicians still addicted to tobacco now refrain from smoking in front of patients, and it is likely that other sections of the profession also appreciate the value of example

But, while the profession should take every opportunity of declaring that smoking menaces health, only effective Government action can decisively influence the general public's attitude In the light of present knowledge, as Fisher [6] has emphasised, it would be hard to justify the Government's continuing laissez-faire policy towards the skilful and sustained propaganda campaign for smoking conducted by the tobacco industry Something must be very wrong when, against the background of a rising death-rate from smoker's cancer, a company can proudly proclaim on television spectacular increases in its cigarette sales

Clearly, anti-smoking campaigns [7] will not induce established smokers to give up the habit, and that is why it is so important to prevent young people from developing this habit The health education officer of Middlesex, Mr W G Penn, recently interviewed 2500 schoolchildren in the county to find out their attitude to smoking [8]

> Boys who smoked started on average at the age of 9 years and girls at 13 Most of the heavy smokers were pupils of lesser ability in secondary modern schools They had no difficulty in obtaining cigarettes, some retailers stock packets of 4 for *6d*, and others sell single cigarettes or even halves They began to smoke usually with others in their home district, rather than with their school companions
>
> In prevention, example was rated highly by the children But three-quarters of them stated that they would accept factual information combined with intelligent persuasion from those they trusted, even if these adults were smokers themselves, provided the adults made it clear that data on the disadvantages were not available when they themselves started smoking Talks on the subject at school were not popular, but science periods, possibly with practical work, or discussion groups, would be acceptable Leaflets were ineffective children did not read them Posters, with one exception—showing a single cigarette with "cancer" spelt out by its smoke—made little appeal
>
> On the negative side, cigarette advertisements on television exerted an influence, but this could be readily dispelled by ironic ridicule
>
> Children appreciate the approach designed to shock them into taking notice—"I don't care if you smoke yourself to death, but if you do smoke you should know the facts" They declared they would gladly watch a film, and, when asked to select a possible plot, chose the one with this approach

Mr Penn recommends that the law prohibiting under-16s from buying cigarettes should be more widely publicised and enforced, and he points to a loophole in legislation this age-group is not prohibited from smoking, but only from obtaining, cigarettes Mathematics teachers, says Mr Penn, should be encouraged to use the figures on smoking and lung cancer when setting problems Posters prepared by the children themselves in art classes could be used for a permanent but changing display Schools' broadcasting and television, he concludes, should at least once a year include programmes on smoking

We agree with the Joint Tuberculosis Council that a policy designed both to reduce cigarette-smoking and, above all, to discourage young people from starting to smoke should be agreed and implemented without delay

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VISCOUNT AMORY, formerly Chancellor of the Exchequer, has been appointed a member of the Medical Research Council, and will succeed the Earl of Limerick as chairman

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[2] Petersen O Precancerous Changes of the Cervical Epithelium Copenhagen 1955

[3] *Tubercle* 1960 41 290

[4] Pyke D A *Brit med J* 1955 i 1115

[5] Cartwright A Martin F M Thomson J G *Brit J prev soc Med* 1960 14 160

[6] Fisher R E W *Lancet* Sept 24 1960 p 710 *ibid* Oct 22 p 9[illegible]

[7] Cartwright A Martin, F M, Thomson, J G *ibid* 1960 i 377

[8] Smoking and Cancer of the Lung *final report of Middlesex County health education officer*, 1959

Special Articles

TREATMENT OF RESPIRATORY PARALYSIS IN SMALL CHILDREN

B W POWELL
M B Cantab , M R C.P , D C H
CONSULTANT PÆDIATRICIAN, PETERBOROUGH AREA

MARY N SMITH
M B Lond , D C H
MEDICAL REGISTRAR, BEDFORD GENERAL HOSPITAL,
LATELY PÆDIATRIC REGISTRAR, PETERBOROUGH AREA

DURING the summers of 1957 and 1958, 11 children, aged from six months to four years, with respiratory paralysis caused by acute poliomyelitis were admitted to the Peterborough Isolation Hospital This is an uncommon condition in the very young, and it is hoped that an account of our experience may help others faced with the same problems

In 1957, 32 patients with poliomyelitis were admitted to the hospital 16 of them were children under fourteen 4 children, all under four, had respiratory paralysis

In 1958, 10 patients with poliomyelitis were admitted There were 2 adults and 8 children 7 of the children, all under three, had respiratory paralysis

Thus, out of a total of 42 patients, 11 (26%) were children with respiratory paralysis There were also 2 adults with respiratory paralysis, making a total of 13 (31%) respiratory cases Of all these, in both years, only 1 child had been immunised against poliomyelitis, having received his second injection three weeks before the onset of the illness

As all cases of poliomyelitis in the area are admitted to this hospital it can be seen that, especially in 1958, there was a high incidence of respiratory paralysis among the younger children This contrasts with the finding of Kelleher et al (1956) who, in a series of 70 cases of acute respiratory poliomyelitis, had no case under one year, 1 under two years, and 7 under five years Neonatal cases have rarely been reported, but McMath (1959) describes a successfully treated case and reviews the literature

SUMMARY OF CASES

—	Case	Age (years months)		Paralysis			Time in respirator (weeks)
				Intercostal	Diaphragm	Other	
1957	A	2	11	+		legs	15
	B	2	11	—		arm	12
	C	4	0	—	—		9
	D	1	0	+		legs	10
1958	E	1	1	+		arms and legs	19
	F	0	6	+		back	39
	G	1	6	+			21
	H	1	11	+		legs	18
	J	1	6	+			10
	K	1	5	+		legs	39
	L	1	1	+		legs	21

The accompanying table summarises our cases

There were also 2 cases of " bulbar " poliomyelitis, but these are not included among the respiratory cases, and none of our respiratory cases had bulbar involvement.

Diagnosis

Respiratory weakness may come on slowly or quickly and at a variable time in the course of the illness The signs, symptoms, and diagnostic tests have been well described by others (Trueta et al 1956, Kelleher et al 1956), but with small children the cooperation of the patient cannot be relied upon, and special tests such as counting and spirometry cannot be used It may, therefore, be difficult in the early stages to decide whether a child is developing respiratory weakness These points have seemed to us the most helpful

(1) *The appearance and behaviour of the child*—At first the child is restless and fretful As the condition progresses, he becomes quieter and weaker but remains wakeful and worried—the " unsleeping apprehension " which Trueta describes The skin may be clammy and pale, and slight cyanosis, difficult to detect by artificial light, sometimes occurs Marked cyanosis is a late sign which occurs only when anoxia is severe The pupils may be dilated, and the pulse-rate and respiration-rate raised

(2) *Respiratory movements*—The respirations become rapid and shallow and, unless the diaphragm is weak as well, there is more abdominal than thoracic movement The upper end of the sternum is drawn inwards with each inspiration, causing a sort of seesaw movement of the sternum In more severe paralysis the accessory muscles of respiration come into use When intercostal paralysis is unilateral or asymmetrical, the difference in movement between the two sides can often be seen Sometimes it is best appreciated by placing both hands round the chest and by feeling the difference rather than by seeing it

(3) *Pulse- and respiration-rates*—Hourly charts, which were of great value, were kept for the first few days in all suspected and established cases of poliomyelitis A rising pulse- or respiration-rate was often an early sign and, in a few cases, it gave us the first indication of respiratory weakness An increasing respiratory-rate is more significant than a rising pulse-rate.

(4) *Biochemical investigations*—Capillary blood-pH determinations and oxymetry were both used, but were not much help in diagnosis They were more useful in the assessment of proper ventilation while in the respirator, and will be discussed later In those cases in which the blood-pH was estimated before putting the child in a respirator, it was never more than 7 2 and it always rose quickly once respiration was assisted Thus it gave some confirmation of the need for going into a respirator

Treatment

Going into a Respirator

One may feel reluctant to put a child in a respirator when the signs are slight and the diagnosis uncertain The following considerations may help

(*a*) Every case of ours developing respiratory weakness eventually needed treatment in a respirator

(*b*) Of the signs and symptoms already discussed, changes in the chest movements are probably the most important, and careful and repeated observation is needed to detect them

(*c*) The respirator may act as a splint for the respiratory muscles Active use of any muscles during the early stages of the disease increases the risk of paralysis in those muscles, and it seems likely that when there is even slight weakness in some of the respiratory muscles the extra strain on those still working normally may dispose to a more severe paralysis

We have concluded, therefore, that once respiratory weakness has been diagnosed, the child should be put into a respirator without delay If there is any doubt, the child should be kept under constant observation by a nurse and frequently examined by a doctor with experience of poliomyelitis cases It is better to err on the side of safety by putting the patient in early than to risk leaving it too late Unpredicted rapid deterioration and collapse can occur, and we had an alarming instance of this Often all doubt was dispelled by seeing the obvious improvement in the child, who after a brief period of anxiety and resistance, settled down gratefully and peacefully to sleep

Management in the Respirator

All our children could be taken out for short periods This simplified nursing problems considerably A watch was kept for retention of urine in the early stages but none of our patients was troubled by this Constipation was often a minor problem, particularly early in the illness when we were trying to get fæcal samples for virus investigation The condition was best treated with glycerin suppositories

A good friction-free seal at the neck is important and the most effective was a dry pad tied round the neck before applying the standard overlapping sponge-rubber collar An ordinary sanitary pad, with, if necessary, a little of the wool-filling removed, was found satisfactory In the earlier cases, 'Vaseline' gauze was tried but the children's necks became sore Necks were never sore when dry pads were used At first, we found that there were no rubber collars available small enough for a baby's neck, but, once the need was known, these were readily obtained

Apart from coping with the physical problems of nursing a small child in a respirator, there are more subtle but equally important aspects of nursing which cannot be ignored Overcoming the initial fears of children and parents, keeping up morale, and maintaining the happiness of the patients during an illness of this sort is no easy task We had a few psychological problems but none was serious For this relative freedom from trouble, we are much indebted to the nursing staff, none of whom had special experience of this type of nursing, and few of whom were "children-trained"

Records

Detailed record-keeping by the nurses was found to be of the greatest help Each patient had a book of his own in which hourly records of the pulse and respiration were kept, the pressure changes in the respirator were noted and a detailed report made This was not only of value in assessing progress but ensured constant and detailed observation of the child It was also one way of helping to train a team of nurses in the management of respiratory paralysis

Types of Respirator

All the children have been nursed in the standard, modified Both respirator, and this has proved satisfactory on the whole

The youngest child was transferred after a few weeks to a Smith-Clark junior respirator, as he seemed unable to breathe well in time with the bigger one The junior respirator, with its higher rate, may be the apparatus of choice in children under three

One alteration suggested is that the front wall of both types of respirator, through which the neck passes, should be made of transparent material It must be frustrating for a child to handle his toys without seeing them, or to see them without being able to handle them—perhaps for months on end

Respirator Rates

It is best with small children to start with the quickest rate attainable and to slow down if necessary This was 28 per minute on the Both respirator and 32 on the Smith-Clark In fact, our patients all settled happily at these maximum rates

Respirator Pressures

On first going in, relatively high pressures were needed, especially when the child was awake Occasionally, it was impossible to get a crying child to breathe with the machine at all, while he was crying the accessory muscles were being used and breathing was quite independent of the respirator and in opposition to it Soon he would become exhausted and would need, and respond to, help from the respirator A sedative, such as chloral, was often helpful

Typical pressures used were −15 0 mm Hg while awake and −10 0 mm Hg during sleep Positive pressures were not used, although the gauge on the apparatus usually swung over to +2 mm Hg

Coming out of the Respirator

All the children we have treated have been able to tolerate short periods out of the respirator, but it was not easy to decide when the length of time out could be increased We thought it unwise to try any increase during the first three weeks After this, the time out was gradually increased, the child himself being the best guide to progress In some children it was immediately obvious if they were out for too long they quickly became pale and tired, and, as soon as they were put back again, lapsed into sleep Others were less easy to assess and we soon learnt to rely largely on the opinion of the sister-in-charge as to whether they had been out too long Looking tired was the commonest sign, and we tried to adjust the time out so that the child was put back before any signs of strain occurred

Later, when we had a better idea of an individual child's behaviour, he was deliberately left out for as long as it was judged that he could tolerate This test period was tried about once a week and, if used with care, was a useful guide to how quickly we could increase the time out, the object being to find the maximum period, short of intolerance Once a child had been out for several hours at a time, he could soon be left out for the whole day

The increase in time was, therefore, done cautiously and slowly at first and more quickly later One particular child showed delayed effects of being out of the respirator for too long He seemed well immediately after a test period of several hours, but looked tired, pale, and unwell for the next two days In this case, oxymetry showed clearly that he had been underbreathing, although there were no immediate clinical signs This delayed reaction was exceptional and on the whole there was a good correlation between clinical findings and oxymetry results

Biochemical Control

In adults the estimation of vital capacity by spirometry may be used for initial diagnosis or for assessment of ventilation while in a respirator This was considered impracticable with very young children and we did not try it, although Walley (1959) described it as a helpful procedure in an eighteen-month-old child The rebreathing method of estimating alveolar pCO$_2$ (Campbell 1960) may prove to be valuable

After consideration of the investigations available to us at the time, we decided that oxygen saturation and blood-pH were the most useful and caused least distress to the child, these were carried out on all our patients

Oxygen Saturation

Oxygen saturation was estimated by means of a 'Stanco' oxymeter mark 2, using the lobe of the ear treated with a rubifacient The results obtained in this way were not necessarily accurate, but any change which occurred before and after a child was placed in, or taken out of, a respirator gave a good indication of whether ventilation was adequate

The oxygen saturation of the blood does not fall much until a considerable degree of respiratory failure has occurred and its greatest use was in assessing how much time could be allowed out during the " weaning " period

A falling oxygen-saturation during a given period indicated that the child had been out of the respirator long enough, the fall occurring before the clinical signs of fatigue set in It was also used as a check on under-ventilation while in a respirator

Blood-pH

This was measured on a heparinised capillary sample taken under paraffin 0 5 ml or more was taken from an ear lobe and made up to 5 ml with distilled water The estimation was made on a Pye pH-meter The sample was particularly easy to obtain if it was taken soon after the rubefacient mentioned above had been applied

The results obtained confirmed the diagnosis and helped us in the early stages of treatment to find the optimum respirator-pressure and to avoid hyperventilation Later frequent estimations were unnecessary

Physiotherapy

Physiotherapy was started for the affected muscles, other than respiratory, as soon as the acute phase of the illness was over The age of our patients made active physiotherapy for their chests difficult, and one of our greatest assets was a skilled pædiatric chest physiotherapist Very young children soon acquired a habit of abdominal breathing which persisted after recovery of the chest muscles, and recovery of chest movements was delayed long after it seemed that there was a reasonable return of power to the intercostals Once the child could be re-educated in correct breathing there was often a rapid improvement

We have had much discussion with our colleagues about the use of abdominal binders We think now that one function of the respirator is to protect the intercostal muscles from movement by acting as a splint We have been content to allow free abdominal movement and have observed that in a respirator the movement is almost entirely abdominal Later, when we have wished to encourage active chest movements, a binder was applied in some cases but it is doubtful if this can be made to reduce the diaphragmatic excursion without also restricting movement of the lower ribs Some sort of corset is needed which will fit over the anterior abdominal wall and up into the epigastrium without constricting the lower part of the chest An attempt was made to construct a suitable corset but it seemed of little use

The opposing view is that thoracic movement should be encouraged, and abdominal distension avoided, by early application of a binder Abdominal distension does occur, but in our children it was not troublesome and follow-up has shown that it never persisted

Follow-up

All the children have been followed up and are doing well They are all out of respirators and living a normal life at home, apart from the unfortunate few with other paralyses Prophylactic penicillin or sulphonamides have been given to protect against respiratory infections It is difficult to say how much good this has done, but none of them has had a severe infection since returning home, and more than one parent has remarked on the relative freedom from colds

Teamwork

Finally, we would like to stress the importance of a combined team in caring for these difficult cases Anæsthetists, orthopædic surgeons, pathologists, physiotherapists, nursing staff, engineers, and electricians all have much to contribute, and we have been especially fortunate in being able to call freely on our colleagues for help and advice Much of what we have learnt, and reported here, is the result of our combined experience, and of discussion with others of individual problems as they arose

Summary

The diagnosis of respiratory paralysis in young children and its treatment are discussed The main points which arise out of our experience with these children are

(1) The importance of early diagnosis of respiratory paralysis and the early use of a respirator

(2) The value of clinical observation and the limited use of biochemical investigations in diagnosis

(3) The function of the respirator as a splint as well as an aid to respiration

(4) The importance of teamwork, and of skilled nursing and physiotherapy

We have had help from many quarters, but we are especially grateful to Dr R E Loder, consultant anæsthetist, Mr Noel Smith, consultant orthopædic surgeon, Sister Course and the many nurses who have worked under her, and Miss Hardy and her fellow physiotherapists

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STERILISATION BY STEAM UNDER INCREASED PRESSURE

A SECOND COMMUNICATION TO THE MEDICAL RESEARCH COUNCIL BY THE WORKING PARTY ON PRESSURE-STEAM STERILISERS *

THE working party began its investigations in 1957 and early last year published a report [1] which re-examined the requirements for efficient sterilisation by steam under pressure, described the principles and technical procedures of sterilisation by this method, and discussed their practical application. Since that time more information, some of it yet to be published, has become available, and further comment on four matters of immediate importance may be helpful

(1) *High-vacuum Dressing Sterilisers*

The need for an initial vacuum down to an absolute pressure of 20 mm Hg or less has been confirmed by several workers and this recommendation is now incorporated in two recent specifications by the British Standards Institution.[2] Well over 100 such sterilisers have been installed in the United Kingdom and experience indicates that, in general, they are proving bacteriologically efficient and mechanically reliable, though with increasing experience minor modifications in constructional detail are being made. The working party wishes to emphasise the potentially greater output, of a high-vacuum steriliser, as compared with other apparatus of the same cubic capacity. Accordingly, when planning for new equipment, the new machine may be of much smaller cubic capacity than the old.[3] Planners should take into account the present trend towards the centralisation of sterilising capacity within a central sterile supply service. In this way space can be saved and expensive equipment utilised fully.[4]

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* The members of the working party are Prof J W HOWIE, M.D , chairman, Dr V D ALLISON, Dr J H BOWIE, Mr E A BRUGES, PH D , Dr E M DARMADY, Dr R J FALLON, Prof ROBERT KNOX, M.D , Dr J A V SHONE, Mr G SYKES, M SC , Prof C A WELLS, F R.C.S , Mr G A P WYLLIE, PH D , Dr J C KELSEY, secretary Address Disinfection Reference Laboratory, Central Public Health Laboratory, Colindale Avenue, London, N W 9

[1] *Lancet*, 1959 i 425

[2] B.S 3219 1960 Horizontal Cylindrical Hospital Sterilisers B S 3220 1960 Horizontal Rectangular Hospital Sterilisers

(2) *High-speed Instrument Sterilisers*

Several of these sterilisers have been installed and we understand they are proving satisfactory in practice. A British Standard[5] has now been published concerning this equipment.

(3) *Air Filters*

In the earlier report attention was drawn to the need to filter the air used to break the vacuum at the end of the sterilising cycle. After examining as yet unpublished work, the working party offer the following suggestions:

(i) *Filter material.*—Filters made of spun glass withstand the wear and tear involved and, if the right grade is chosen, are very efficient. At present glass fibre felted into sheet form of paper thickness offers the best prospects.

(ii) *Penetration.*—The methylene-blue penetration should be not more than 0·003% and could easily be as low as 0·001% without undue increase in resistance.

(iii) *Support.*—The filter material must be held firmly between metal grills for support, to prevent distortion, and to ensure uniformity of efficiency at all air flows. The space requirement for a filter built on these lines is negligible.

(iv) *Filter canister.*—This must be of stout construction in a metal which does not readily corrode (e.g., stainless steel or tin-plated brass).

(v) *Flow control.*—The incorporation of a critical orifice to ensure uniformity of flow and prevent excessive strain on the filter would be advantageous and very easily applied.

A filter built on these lines might be expected to have a working life of at least 12 months before requiring to be re-packed and need cost little, if anything, more than many filters now in use which are of much lower efficiency. At least two filters which approximate to this specification are already available commercially.[6]

The use of cotton-wool in cups or tubes cannot now be considered as more than an interim measure. The wool, which must be sterile and dry, needs to be changed frequently and unless it is firmly compressed channels form in it with loss of filtration efficiency.

(4) *Sterilisation of Rubber Gloves*

Work on this subject is in progress in several centres. The information available to the working party to date indicates that gloves may be sterilised in a high-vacuum steriliser at 130–134°C along with dressings, without suffering undue damage.

Great interest in hospital sterilising arrangements has been stimulated by recent publications, including the first report of the working party. It is now clear that the technical requirements for safe and efficient sterilisation by steam under pressure have been well defined, and the four matters of current interest discussed above confirm the views previously expressed by the working party, in particular the requirement for a high pre-vacuum for the sterilisation of dressings.

GENERAL MEDICAL COUNCIL

SESSION NOV. 22–26

IN a presidential address at the opening of the Council's 201st session, Sir DAVID CAMPBELL recalled that both the Council and the Pharmacopœia Commission had been invited to submit evidence to a working party established by the Minister of Health, in consultation with the Home Secretary and the Secretary of State for Scotland, "to review the legislative provisions which relate to the control of medicinal substances, and to recommend what changes should be made to rationalise and simplify the law with a view to ultimate amendment and consolidation."

At present there was no comprehensive and unified system of statutory control of medicinal substances. Many separate controls had been established piecemeal over the years, and were administered by a number of bodies, including the Dangerous Drugs Branch of the Home Office, the Poisons Board, the Ministry of Health, the General Medical Council, and the Pharmaceutical Society. In addition to such statutory controls, certain books of standards prepared on a voluntary basis by the Pharmaceutical Society and the British Medical Association jointly had received official recognition, while other official bodies, such as the Standing Joint Committee on the Classification of Proprietary Preparations and the Joint Committee on Prescribing, had been established for special purposes in the National Health Service.

Under Section 47 of the Medical Act, 1956, which re-enacted provisions going back to the original Act of 1858, the Council was responsible for the publication of the *British Pharmacopœia* which must contain "descriptions of and standards for ... medicines, preparations, materials and articles used in the practice of medicine, surgery, and midwifery."

After full consideration and mutual consultation, the Council and the Commission had reached the conclusion that, as a consequence of recent developments in pharmaceutical practice, it had become desirable to change some of the procedures followed in regard to the *British Pharmacopœia*. Memoranda conveying the views of the Council and the Commission had been conveyed to the working party, which were in substantial agreement.

One of the recommendations related to the status of Approved Names. Since 1940 it had been the practice of the Council, acting on the recommendations of the Commission, to announce from time to time the names by which certain drugs would be described if they were subsequently included in the *Pharmacopœia*. Experience had shown, and the interim report of the Hinchliffe Committee on the Cost of Prescribing had recently attested, that the regular and prompt publication of Approved Names served more than one useful purpose. It helped to avert the use of a number of different names for the same active substance, and it served to protect as far as possible a suitable name from proprietary adoption as a trade mark.

This practice, however, was unofficial. The Commission and the Council thought that, if changes in the law were contemplated, it would be appropriate to accord them statutory recognition. They had accordingly recommended that the Council should receive statutory authority for the issue of Approved Names, and that, while manufacturers should of course be left free to use their own proprietary names, it should not be legal for them to use any unofficial non-proprietary name for a drug other than the Approved Name They had also recommended that manufacturers should be required to indicate the Approved Name of any drug on the labels of the medicine or preparation, and in all advertising matter Such a provision would guard against confusion without seriously inconveniencing the manufacturer

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[3] *Lancet*, Sept. 17, 1960, p. 643.

[4] *ibid.* p. 353.

[5] B.S. 3233: 1960 Pressure Steam Sterilisers of Small Size (with Independent Steam Supply).

[6] F. N. Mackley & Co., Hanks Road, Gateshead 8, Co. Durham; Vokes Ltd., Henley Park, Guildford, Surrey.

The inclusion of a drug in the *Pharmacopœia* had come to be widely accepted as an indication that it was therapeutically reliable, and a number of regulations and provisions, both in this country and overseas, had been framed on this assumption The Council did not wish to disturb this situation At the same time it was conscious that the necessary intervals between the publication of new editions and addenda sometimes caused considerable delay before a pharmacopœial standard was provided for a drug newly introduced into medical practice As a result, some drugs and preparations were widely sold before independent standards had been provided

In these circumstances the Council had been impressed by the view, which was strongly held by the Commission, that in the public interest standards should be made available for all drugs at (or very soon after) the time when the drugs began to be used in medical practice It was true that under the provisions of section 47 of the Medical Act the Council was at present empowered to publish amendments of, and additions to, the *British Pharmacopœia* at any time, and it would be legally in order for it to publish, in the form of addenda to the *Pharmacopœia*, monographs for drugs as soon as they were placed on sale It was advised, however, that such a course would not be equitable, or indeed practicable, in present circumstances The Council and Commission accordingly had made a number of suggestions designed to enable the Council to publish, as Approved Specifications, standards for all newly introduced drugs as soon as, or within a short period after, the drug was placed on sale in the United Kingdom These Approved Specifications would have a definite legal status of their own similar to, but distinct from, the standards given for drugs included in the *British Pharmacopœia* The *British Pharmacopœia* would also continue to be published as at present, and some, but not all, of the drugs for which Approved Specifications had been issued would eventually be absorbed into it

The evidence submitted also touched on two other important topics The first of these related to the statutory authority of the standards contained in the *Pharmacopœia* This was mainly a legal question After comparing the law in this country with that in certain other countries the Council had recommended that the law should be amended to provide that in the United Kingdom any drug which was prescribed or demanded under a title or subsidiary title used in the *Pharmacopœia* should comply with the relevant requirements stated therein

The evidence also dealt with the question of ensuring identity of the standards prescribed in the *British Pharmacopœia* and the regulations of the Therapeutic Substances Act Under existing arrangements it had been possible for divergencies to occur in the standards prescribed for the same substances in the *British Pharmacopœia* on the one hand and the regulations made under the Therapeutic Substances Act on the other In order to avoid such an undesirable duplication of standards, the Council and the Commission had recommended that the Therapeutic Substances Act, or the regulations made thereunder, be amended at the earliest opportunity so as to provide that, where any substance covered by part I of the Act was included in the *Pharmacopœia*, the standards to be observed in respect of that substance, and the tests to be used in determining whether those standards had been attained, should be contained in the *Pharmacopœia*

Presenting the report of the Pharmacopœia Committee, Dr H GUY DAIN, its chairman, said that sales of the last *British Pharmacopœia* and the last *Addendum* (32,024 and 4970), compared with those of the previous *Pharmacopœia* and *Addendum*, showed a considerable falling off in accordance with the alteration in retail pharmacy, which would continue There was not the same need for the retail pharmacist to be in possession of the *Pharmacopœia*, which set out the standards for making up prescriptions, because he was supplied by the manufacturer with drugs to the laid-down standard

Turning to the section of the Pharmacopœia Commission's report which stated that the Commission continued its efforts to make possible the abandonment of the apothecaries system of weights and measures in the next edition, Dr Dain explained that the change could not be made without an Act of Parliament because under the present law the pharmacist must do exactly what the prescription stated and it would be impossible for him to dispense in the metric system a prescription made out in the apothecaries system The Government's new weights and measures Bill introduced the metric system not only for medicine but for everything else, but this would not be put into effect before 1967 " We are anxious to make the progress we want to make in 1963", continued Dr Dain, and he announced that Lord Cohen of Birkenhead had undertaken to move an amendment in the House of Lords

The revision of legislation concerning medicines was, said Dr Dain, " a matter on which we are not too happy " The control of medicines was governed by a number of Acts, and the Government had set up an interdepartmental committee to look at the matter, but the terms of reference were so wide that some anxiety was felt as to what might emerge The Council itself and the Pharmacopœia Commission had issued their views to the committee, but they were very anxious that everything should be done to consolidate the Acts and make sure that the position of the *Pharmacopœia* and the Commission in the matter was properly assured

At its May meeting in 1959 the Council asked each licensing body and medical school to submit not later than March 31, 1960, a statement with regard to its courses of study and examinations, together with an indication of any changes which had been made or were under consideration for the purpose of giving effect to the revised recommendations Last May the Council gave preliminary consideration to the statements so far received and decided to adjourn further consideration until the present meeting But the PRESIDENT announced that not all the licensing bodies and medical schools had yet submitted statements At his suggestion a committee of deans and former deans was set up to analyse the statements and extract from them anything in the nature of a new approach and to report to the May, 1961, meeting

Medical Disciplinary Committee

The committee met on Nov 23–26, under the chairmanship of the President

APPLICATIONS FOR RESTORATION

The Registrar was directed to restore to the Register the name of Alexander Gordon Bonnyman The committee refused the applications of John Bodkin Adams and Peter William Spencer Gray

REMOVAL FROM REGISTER

Harold John Salter, registered as of Oakwood Hospital, Maidstone, Kent, M B Lond (1954), was charged with behaving improperly to and committing adultery with a woman patient The committee determined the facts alleged proved to their satisfaction that the doctor was guilty of infamous conduct in a professional respect, and directed the Registrar to erase from the Register the name of Harold John Salter He has 28 days in which to appeal to the Privy Council

James Albert De Gregory, registered as of Tudor Villa, Vaughan Street, Rhyl, Flintshire, M B Edin (1931), was alleged to have been the family doctor of a man and his wife and subsequently of their three children and continuing to stand in professional relationship with the woman until Dec 9, 1958, when her name was transferred, and with the remaining members of the family It was further alleged that after he had entered into professional relationship with the man and wife and their family he improperly associated with the wife and from a date in or about December, 1958 (subsequently amended to July, 1959) he frequently committed adultery with her, and that he was found guilty of adultery with the woman by decree of the divorce court made absolute on May 25, 1960 The committee found Dr De Gregory guilty of infamous conduct in a professional respect in regard to the facts found proved against him and directed the Registrar to erase from the Register the name of James Albert De Gregory He has 28 days in which to appeal

William David Smith, registered as of 118, Marlborough Park Central, Belfast, M B Belf (1940), originally had judgment postponed for a year in November, 1957, following convictions in 1956 and 1957 for being in charge of a motorcar while under the influence of drink or drugs In November, 1958, the committee were not satisfied that the evidence so far received would warrant their discharging the case and postponed judgment for a further six months At the meeting in May, 1959, a further charge of driving while under the influence of drink was proved In order, however, to give him one further opportunity of overcoming his tendency to indulgence in drink, judgment was postponed for a year Last May the committee were informed of a further charge of being drunk in charge and postponed judgment to the present session so that they might be aware of the result of these proceedings He had been convicted of this offence at Oxford Quarter Sessions and sentenced to three months' imprisonment, ordered to pay £50 costs, and disqualified for 10 years Announcing that the Registrar had been directed to erase from the Register the name of William David Smith, the chairman said "The committee think on the whole that it is a kindness that they should remove your name from the Register for the time being, but if you come before them again cured of your addiction to drink, application for the restoration of your name to the Register will be sympathetically considered" Dr Smith has 28 days in which to appeal

Archibald Thomas Macmaster Glen, registered as of 25, Santos Road, London, S W 18, L R C P E (1935), had judgment postponed for a year in May, 1959, following convictions in that year for driving a car under the influence of drink and being drunk and disorderly, the chairman saying that in the light of his previous record the committee regarded with grave concern the further offences of which he had been convicted When he came for postponed judgment he had been convicted again of being drunk and disorderly The case was adjourned for a further six months A further charge was now found proved, of being drunk in a public place, for which he had been fined 20*s* at the South-Western Magistrates' Court last July The Registrar was directed to erase from the Register the name of Archibald Thomas Macmaster Glen, the chairman telling him, in similar terms to those used in Dr Smith's case, that they thought on the whole this was a kindness He has 28 days in which to appeal

Mrs Grace Alison McCormack, registered as of 70, Cheriton Square, Balham, London, S W 17, M R C S (1940), was charged with having been convicted at Coalville Magistrates' Court in 1955 on four charges of unlawfully procuring dangerous drugs and one of failing to keep a Dangerous Drugs Register, for which she was fined £125 and ordered to pay £6 15*s* costs, and infamous conduct in a professional respect in that she had between various dates in December, 1958, and January, 1959, obtained morphine at Bundarra, New South Wales, for the purpose of gratifying her own addiction, by fraudulently representing that she had prescribed them for various patients, and at Bundarra administering morphine to herself, to which offence against the Police Offences (Amendment) Act, 1908, of New South Wales she had pleaded guilty Ordering the erasure of the name of Grace Alison McCormack from the Register, the chairman observed that this did not prevent her from applying for restoration if she was cured She has 28 days in which to appeal

James Albert Seavers, registered as of 45, Clerkenwell Close, Finsbury, London, E C 1, M B N U I (1939), was charged with having been convicted of indecent assault for which on Aug 22, at Lambeth Magistrate's Court, he was sentenced to three months' imprisonment By reason of the conviction the Registrar was directed to remove from the Register the name of James Albert Seavers He has 28 days in which to appeal

CASE DISMISSED

Andrew Edwin Beith, registered as of 17, Lincoln Street, Leicester, M R C S (1924), was charged that, being registered under the Medical Acts and having undertaken to provide general medical services under the National Health Service, on *July 30, 1955,* he failed without reasonable cause to visit and treat Anita Jane Beighton (aged 14 months) whose condition so required and for whose treatment he was responsible under the National Health Service, and that during a period between Feb 27 and March 27, 1959, he failed without reasonable cause to visit and treat the late Mrs Grace Annie Rose Spencer whose condition so required and for whose treatment he was responsible under the National Health Service The charge continued "By your conduct as aforesaid you neglected your duties as a medical practitioner under the National Health Service and disregarded your personal responsibilities to the patients whom you had accepted on your list, and that in relation to the facts alleged you have been guilty of infamous conduct in a professional respect" The committee determined that the facts alleged against Dr Beith had been proved to their satisfaction They considered these facts to be regrettable, but came to the conclusion that they did not constitute infamous conduct in a professional respect, and they recorded a finding that Dr Beith was not guilty of infamous conduct in a professional respect

CASES POSTPONED

In the absence of any evidence concerning the habits and conduct of Florence Berchmans Lawlor, registered as of 50, Beaumont Street, London, W 1, M B N U I (1936), against whom judgment had been postponed for a year following convictions for being in charge of a motorcar when under the influence of drink in 1960 and unlawfully obtaining drugs by *false pretences in 1959, the committee did not feel justified in* discharging the case at present and therefore postponed judgment for a further six months, until May 1961

The committee were not satisfied that the evidence produced on behalf of Richard Maurice Dooley, registered as of 74 Eglinton Road, Donnybrook, Dublin, M B Dubl (1945), would warrant them discharging the case at present They therefore postponed judgment for a further six months on four convictions involving drink

William Quirke, registered as of Mountjoy Lodge, Kildare, L R C P I (1949), was charged with having been convicted on two charges of obtaining drugs by false pretences and one of unlawfully procuring dangerous drugs for which at the Castleford West Riding Magistrates' Court on June 1, 1960, he was fined £100. Judgment was postponed for a year.

Alfred Francon Williams, registered as of 18, Crabtree Lane, Sheffield 5, M.B. Edin. (1940), was charged with having been convicted at Sheffield Magistrate's Court on July 19, 1960, of being drunk in a public place, when he was fined 10s. and ordered to pay 7s. 6d. costs, and of a like offence at the same court on Sept. 19, when he was fined £1. Judgment was postponed for a year.

Henry Joseph Caron, registered as of The Surgery, Tyntyla Road, Llwynypia, Rhondda, Glam., L.A.H. Dubl. (1949), admitted a conviction at Ystrad Magistrates' Court on eight charges of unlawfully procuring dangerous drugs, for which he was fined £200 and ordered to pay £10 10s. costs. Judgment was postponed for one year.

CASES CLOSED

The committee determined that the Registrar should not be directed to erase the names of Henry Stanley Marshall Perera, L.R.C.P.E. (1959), registered as of Daisy Hill Hospital, Newry, Co. Down, of Geoffrey Roderick Richards, M.R.C.S. (1937), registered as of 5, Corrymore Mansions, Sketty Road, Swansea, and of George Lewis Minter, M.B. Edin. (1950), registered as of 133, Queen's Road, Blackburn, Lancashire. In each of these cases judgment had previously been postponed.

CASE HELD OVER

The case of Loh Mung Sun, registered as of 25, Channel Road, Sibu, Sarawak, Borneo, L.R.C.P.E. (1917), was postponed to the next meeting of the committee.

Symposium

ANTICOAGULANT THERAPY

FROM A CORRESPONDENT

A symposium on Anticoagulant Therapy was held in London on Nov. 18 and 19.

Reviewing laboratory control, Dr R. P. Biggs (Oxford) said that the coumarin anticoagulant drugs cause a fall in the blood level of factors VII, IX, and X, and of prothrombin, and influence the adhesiveness of platelets; factors V and VIII are unchanged. She suggested that the responsibility of the laboratory worker is primarily to ensure that the levels of these factors never fall so low as to cause hæmorrhage; in other words, he should prevent the clinician from allowing these drugs to degenerate into hæmorrhagic poisons. The one-stage prothrombin test is widely used, for, by and large, it distinguishes safe from unsafe levels of treatment. The drawbacks of this test are its insensitivity to small deviations from normal and the technical effect of different sources of tissue-extract on the results. The prothrombin and proconvertin method is more sensitive in the near normal range, but this test still requires carefully standardised reagents. The thrombotest method provides a standardised reagent and seems the most suitable for routine use in small laboratories.

In the past ten years Prof. P. A. Owren (Oslo) has pioneered a large-scale and expanding programme of lifelong prophylactic anticoagulant therapy in Norway, and he introduced the thrombotest in response to the need for a simple and reliable test to subserve this programme under variable laboratory conditions throughout the country. Dr W. Walker (Dundee) has confirmed its value and recommends that capillary blood be obtained by a scalpel wound of the lateral aspect of a finger. The thrombotest method is apparently ideal for the control of anticoagulant therapy in, for instance, the small rural Australian communities with limited laboratory facilities described by Sir William Morrow (Sydney). Long-term anticoagulant therapy would be extremely hazardous or even impossible under these circumstances but for well-organised flying-doctor services and the keen enthusiasm of country practitioners who contend with their own laboratory techniques.

Professor Owren's Norwegian programme of life-long anticoagulant therapy embraces rheumatic heart-disease with embolism, angina pectoris of less than two years' duration, myocardial infarction after the first attack, and thrombosing atherosclerosis of the legs and of the cerebral circulation. Support of the value of such a regime in myocardial ischæmia was forthcoming from Dr A. S. Douglas (Glasgow), who cited the results of the Medical Research Council's long-term anticoagulant trial, from Dr M. M. Suzman (Johannesburg), who found that the fatality-rate fell from 54% to 22% with prolonged therapy, and from Dr Paul Wood (London), who observed that the mortality among treated cases of coronary insufficiency is a fifth of that in the controls. Dr Wood felt that patients repeat their pattern of onset of symptoms, and this provides some guidance in the selection of cases for long-term anticoagulant treatment. Patients in whom severe symptoms developed suddenly are liable to have this experience again without warning, so for these it seems advisable and safer to continue on long-term anticoagulants, whereas those in whom adequate warning is given by crescendo angina of effort can be controlled as symptoms arise. Dr Wood suggested that all patients receiving anticoagulants should carry cards indicating the dosage and serial prothrombin-times. Dr H. Lempert (Manchester) disagreed, for the introspective can be profoundly anxious over minor variations in these readings. Those who have endeavoured to console introspective rheumatoid patients over minor fluctuations in their erythrocyte-sedimentation rates will sympathise with Dr Lempert's viewpoint. Most would agree with Dr Wood and with Prof. R. B. Hunter (Dundee) that the ultimate responsibility for the control of treatment, although dictated by laboratory means, lies with the clinician.

Dr Douglas has questioned 30 doctors covering a population of 70,000 in the environs of Glasgow to assess the number of patients who had sustained one myocardial infarct or who had effort angina. From this survey, it seems likely that about 10% of the population would need long-term anticoagulants. Dr M. F. Oliver (Edinburgh) has calculated that such an incidence would cost the country £1 million annually. But Professor Owren pointed out that this stressed the debit without taking into account the large credit side of lessened mortality and morbidity. Dr Oliver supported this by citing worth-while expenditure of £6 million on poliomyelitis immunisation. Dr J. L. Stafford estimated that the service costs £1 per patient's visit to St. George's Hospital, London, and Dr Stark Murray that the domiciliary service in the Kingston area costs £1 per test.

Anticoagulant therapy is not free of danger. Dr R. W. Emmanuel (London) mentioned an increased risk of fatal hæmorrhage in Eisenmenger's syndrome and Dr John Marshall has dealt with some instances of complicating cerebral hæmorrhage. Prof. Sheila Sherlock (London) enjoined caution in its use in patients with liver disease. Failure of blood coagulation is a recognised complication of jaundice and hepatocellular dysfunction, and when congestive hepatomegaly develops in patients receiving anticoagulant therapy their prothrombin-times may rise to alarming levels and hæmorrhage may ensue. Nonetheless, liver disease need be no bar to anticoagulant therapy so long as careful laboratory control of blood-clotting and of liver-cell function is maintained. She drew attention to the rarity of intravascular thrombosis and atherosclerosis in patients with chronic parenchymatous liver disease, and indicated that this observation may prove to be a growing-point in our better understanding of these phenomena. Although the cirrhotic may be spared the sequelæ of atherosclerosis and myocardial ischæmia this cannot be construed as a good argument for alcoholism.

The proceedings of this conference are to be published by Harvey & Blythe, Ltd.

In England Now

A Running Commentary by Peripatetic Correspondents

I SHALL never understand how a people who set as much store by comfort as do the Americans—with their big, well-sprung cars, centrally heated homes, and air-conditioned offices—can tolerate and even encourage shower-baths. In many places where they live there is either no tub at all or else one of such curious shape and meagre dimensions that it is all but impossible to use it in any position save the erect. I note that that great critic, Mr. Edmund Wilson, who claims that he has had more "uplifting thoughts, creative and expansive visions" in American bathrooms than in European cathedrals, speaks of "soaking in comfortable baths or drying myself after bracing showers." He does not pretend that showers are comfortable.

When you turn on a shower, nine times out of ten your arm must be in the line of the shower if you are to reach the tap. The initial unavoidable blast of cold water is not so bad, but if you have misjudged the proportions of hot and cold, your arm will be exposed to another cold blast, or else a scalding one, when it timidly reaches out to readjust the tap. This procedure often has to be repeated several times. It is usually possible to step into the shower backwards to avoid the flood on your face and eyes—though hazardous if the floor is as slippery as it is in nine showers out of ten. Some showers are almost large enough for you to bend over and wash your feet without striking your head on the wall. Some even have a receptacle for the soap, in the others you have to hold it in your hand all the time or keep retrieving it from the floor. In cold weather a tub will surround you with delicious warmth, like central heating, not so the shower. It is very difficult to get the water to run down your back and front simultaneously, and in general the effect is like that of the Old World's coal fire—you are comfortable (if not burned) on one side and frozen on the other. If the water is too cold, and you are foolhardy enough to try and adjust it, you will usually find that the hot-water tap is so sensitive that the least touch will cause it to eject a jet at scalding temperature. Worse, there may be temperature changes beyond your control—in the words of Vladimir Nabokov, showers have "one definitely neo-Laodicean characteristic in common, a propensity, while in use, to turn instantly beastly hot or blindingly cold on you, depending on whether your neighbour turned on his cold or his hot to deprive you of a necessary complement in the shower you had so carefully blended."

It is argued in favour of showers, first, that they use up less of the community's water than a tub bath—an assertion that I disproved by taking a shower in a tub with the plughole plugged and finding the water near to overflowing long before I had finished, and second, that you get cleaner than you would in a tub, sitting in water that gets dirtier and dirtier. There may be some truth in this, if you are really dirty—after, say, shovelling a couple of tons of coal from one bunker into another, but then not many Americans are often in this predicament. If, however, they come to realise how close in comfort coal fires are to their beloved showers, perhaps more of them will be.

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Some years ago, when we were working with rabbits, we injudiciously bought a pair of electric clippers to facilitate cutting their hair. This apparently put us on the mailing-list of all the hairdressers' suppliers in Britain, and we have been bombarded and even pursued abroad by letters containing special Easter offers to trade in our worn-out scissors or telling us how to get another *3d.* or *6d.* on every haircut without having to spend any money on extra equipment or supplies. We have been offered large plastic stimulators and small rubber vibrators. "Bring more money into the saloon!" the postcards cry. Now that our local hairdressers' charges have gone up for the third time in two years, we are seriously thinking of trying it out. We have for some time been trimming the hair of our children with the rabbit clippers, and have acquired some small skill. In fact, last week we trimmed our rather shaggy cocker spaniel to perfection. It is only a question of changing over to bigger game, and we have offered, for half the official price, to cut the hair of our new graduate assistant in a saloon we have established off the feed-room in the animal house.

• • •

I now have no doubt that a country cottage is the best antidote to a consultant's life in a large industrial city. Stepping over the threshold seems to induce relaxation.

It isn't like the Ritz, and indeed the farm worker viewed it as unfit for human habitation and says that he's happier in the modern bungalow which has been built for him. With this excuse we have eagerly seized the cottage, and put it into good shape, mainly with our own hands. It is timbered, black and white, and built about 1640, and the presence of electricity enables us to rough it with electric blankets and other comforts when necessary. So far only one thing has marred it. The mental tranquillity of the Sunday has sometimes been replaced on the Monday morning, during Outpatients, by a humiliating looseness of the bowels.

I had thought of consulting a psychiatrist, as it seemed an obvious escape mechanism, symbolising an unconscious desire to rid myself of the humdrum of routine work. But serious consideration will now have to be given to an alternative diagnosis. I've just discovered that there is a dead horse in our water-supply.

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Driving home on my weekend off, I was stopped by a herd of cows. After ten minutes of stopping and starting I began to infiltrate. The occupants of two cars going the opposite way looked at me rather oddly and one shouted something which sounded rude, but was unfortunately unintelligible. I stopped to allow a large bull to move out of the way and then started again. The car jolted, shook, and stalled. A large pothole, I thought—strange I hadn't noticed it. I started again, using the accelerator more strongly, the car rocked violently and stalled again. It had never behaved like this before, it felt alive. At that moment a soldier in an army truck climbed down and came to my window. "Excuse me, miss," he said, "but did you know—er, can I help you—you have a cow in your back bumper."

• • •

In the course of moving house in a northern purse-sparing community, I had to throw out a cupboard-full of old and more or less mutilated medical journals. My wife offered some samples to the local fishmonger. I am sorry to report that *The Lancet* came out of this test badly. "Nae, nae, the paper is o'er absorbent, and moreover the reading matter is too intellectual for most of my customers." However a stack of a sister journal was accepted with gratitude. "They'll do fine, good waterproof paper and plenty of interesting pictures, some in colour forbye."

• • •

The formal advertisement for an exchange of practices which you carry this week is the outcome of my dream of finding some way to get out of my routine life and to spend a sabbatical spell in some totally different environment. My practice is in rural Western North Dakota where there is grain-farming, ranching, oil drilling, and American Indians. The nearest large town is 70 miles away and the nearest hospital 32 miles. I have the rather large investment of a 5-bedroom home and an 8-room clinic (surgery) (X-ray, E.C.G., lab., &c.) with 3–8 year records on over 4500 people. Now there must be some doctor in Great Britain, like me, in his late thirties who is tied down with family and commitments and investments, who has had his nose to the grindstone since he left hospital work and his formal medical training, who has been seeing the same faces year in and year out until he wonders where it is all leading! Such a man I would like to step into my shoes, and I in turn would take over his practice. He could make my family and me very happy and at the same provide his own family and himself with an interesting opportunity for educational growth.

I wonder if I am your first peripatetic advertiser?

Letters to the Editor

"THEY NEVER TELL YOU ANYTHING"

SIR,—" Of course, they never tell you anything in hospital " is, as Dr Donaldson (Nov 26) points out, a common remark of those who leave hospital, and is used by him and often by others, writing to the newspapers, as a stick to beat the hospital staff Yet I think there are very good reasons why this statement, so often made, should not be taken at its face value, because I have long been interested in trying to find out exactly what it is that the patient has *not* been told It is a most interesting aspect of the whole subject of doctor-patient communication, and considering how much the communication from patient to doctor (i e, the evaluation of symptoms) is discussed it is odd how little attention is paid to the process in the opposite direction, the process of explanation, and how often it fails completely

One finds this when one talks to patients after their return home from hospital Most people are only too willing to talk of their operation, and while they often preface their remarks with " of course, they never tell you anything in hospital ", it becomes obvious as they go on that, in fact, many people have taken great pains to tell them a lot These patients certainly have no intention of telling a direct lie and would be horrified if they thought their remarks implied adverse criticism they are generally grateful and " of course, the doctors and nurses were all marvellous " These same people with equal innocence often attribute to me, or my partners, remarks which we never made, and it must be familiar to all of us to hear with horror and wonder the things we are supposed to have said, that meningitis is due to thinking too hard, that someone is thin because threadworms eat up all their food, or that if the swelling of the ankles spreads up to the body the heart will stop All these remarks have been attributed—incorrectly, I may say—to myself, and by patients who bear no antagonism and have no wish to slander me This is just another example of failure of communication

This failure arises chiefly, I believe, from failing to realise exactly how difficult the process of communication is, and that to most patients the simplest fundamentals of anatomy and pathology are as obscure as the fundamentals of an electronic computer are to me It is not a question of intelligence, but of familiarity, and our constant day-to-day preoccupation with medicine dulls our appreciation of the obscurity of that diagram of gallbladder and common bileduct which we draw to explain to our patient his pain and his jaundice Try and imagine a technician drawing a diagram to explain why your electronic computer can't add two and two when you don't even know what an electronic cell is

This is only one aspect of the subject Failure to discover and deal with hidden fears is another Even more important perhaps, we may forget how much of hospital routine we take for granted—the intravenous drip, the tube up the nose, starvation before operation, the white sheet on the abdomen that must not be touched, pubic shaving, the first sight of a gleaming Boyle's machine, the unannounced technician with a 10 ml syringe, the groans of the chap in the next bed, just back from theatre who sounds as if he is in agony even if he isn't Very often the " anything " that ' they never tell you " is the routine happenings of the ward, because to the staff it is ordinary common or garden *dull* routine—routine to the staff but a new and potentially terrifying series of experiences to the patient

Finally there is the positive desire not to understand, in order to preserve at all costs the magic of the hospital so that it can work miracles if miracles are necessary This most certainly exists, though it is too large a subject to expand on here It is common in the elderly and it does explain why the remark ' they never tell you anything ' is so often voiced, not as a grumble, but with positive pleasure and as a mark of gratitude for services rendered

Thus there are good reasons for believing in the first place that the remark " of course they never tell you anything in hospital " is just not true in its literal sense, and in the second place that simple measures like allotting to student, houseman, or registrar the job of " telling the patient, in simple lay terms " will do little to overcome the frequency with which the remark is heard

Wantage,
Berks

I S L LOUDON

SIR,—Dr Donaldson oversimplifies the problem of telling patients about their illnesses when he says " someone " should tell " every patient " before leaving hospital what is wrong with them He is dogmatic in implying that this is necessarily an important part of their treatment, and, I suggest, misguided if, in this context, he agrees with Emerson that " knowledge is the antidote to fear "

Like many housemen, I have been that " somebody " for a year now I regard explanation to patients as, in large part, the houseman's responsibility and have tried conscientiously to deal with the problem, but I don't think I have evolved any satisfactory method

Even with non-malignant disease it is far from easy While agreeing with Dr Donaldson that, too often, a patient is given inadequate information, it is remarkably difficult to explain to a layman anything except the simplest of diseases On many occasions the consultant, the registrar, and I have given careful explanations to patients, only to find by the questions asked later that virtually nothing has been grasped of what has been said

Malignant disease presents an even more difficult problem Some patients undoubtedly wish to know what is wrong with them no matter what the implication Personally, I think this a comparatively small proportion, but they should be told Others show by their discussion both with doctors and nurses, or by their avoidance of discussion, or refusal to face up to manifest evidence of physical deterioration, that they do not want to be told anything I have seen the personalities of such patients disintegrate at having unwanted explanation thrust upon them Others purport to want to know, but, by the way they word their questions, do not want the truth How else can one interpret the question " I haven't got cancer, have I doctor? " Is the correct reply to this " yes "—however circumlocuted? It is simply not true, in my experience, that " very seldom will a ' white lie ' have to be told " to a patient It is necessary quite often

Telling patients about their illnesses is not something that can be managed by any rule-of-thumb Human beings must be judged individually According to the ability of the doctor to do this astutely, so will he be able to decide on the form of explanation suited to each patient

London, W 1

SIDNEY CROWN

DRUG DOSAGE FOR INFANTS

SIR,—Your annotation of Oct 29 drew attention to a formula based on surface-area The method, which involved the calculation of the 0 7 power of the weight in kilogrammes, was said to be " both convenient and accurate " Before we all rush for logarithm tables and slide-rules, it would be as well to examine these claims

The convenience of a method is always a matter of opinion I venture to suggest that the use of a nomogram has much to commend it (Incidentally, poor mathematician that I am, to

In England Now

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I SHALL never understand how a people who set as much store by comfort as do the Americans—with their big, well-sprung cars, centrally heated homes, and air-conditioned offices—can tolerate and even encourage shower-baths In many places where they live there is either no tub at all or else one of such curious shape and meagre dimensions that it is all but impossible to use it in any position save the erect I note that that great critic, Mr Edmund Wilson, who claims that he has had more "uplifting thoughts, creative and expansive visions" in American bathrooms than in European cathedrals, speaks of "soaking in comfortable baths or drying myself after bracing showers" He does not pretend that showers are comfortable

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This failure arises chiefly, I believe, from failing to realise exactly how difficult the process of communication is, and that to most patients the simplest fundamentals of anatomy and pathology are as obscure as the fundamentals of an electronic computer are to me It is not a question of intelligence, but of familiarity, and our constant day-to-day preoccupation with medicine dulls our appreciation of the obscurity of that diagram of gallbladder and common bileduct which we draw to explain to our patient his pain and his jaundice Try and imagine a technician drawing a diagram to explain why your electronic computer can’t add two and two when you don’t even know what an electronic cell is

This is only one aspect of the subject Failure to discover and deal with hidden fears is another Even more important perhaps, we may forget how much of hospital routine we take for granted—the intravenous drip, the tube up the nose, starvation before operation, the white sheet on the abdomen that must not be touched, pubic shaving, the first sight of a gleaming Boyle’s machine, the unannounced technician with a 10 ml syringe, the groans of the chap in the next bed, just back from theatre who sounds as if he is in agony even if he isn’t Very often the “ anything ” that “ they never tell you ” is the routine happenings of the ward, because to the staff it is ordinary common or garden *dull* routine—routine to the staff but a new and potentially terrifying series of experiences to the patient

Finally there is the positive desire not to understand, in order to preserve at all costs the magic of the hospital so that it can work miracles if miracles are necessary This most certainly exists, though it is too large a subject to expand on here It is common in the elderly and it does explain why the remark “ they never tell you anything ” is so often voiced, not as a grumble, but with positive pleasure and as a mark of gratitude for services rendered

Thus there are good reasons for believing in the first place that the remark “ of course they never tell you anything in hospital ” is just not true in its literal sense, and in the second place that simple measures like allotting to student, houseman, or registrar the job of “ telling the patient, in simple lay terms ” will do little to overcome the frequency with which the remark is heard

Wantage,
Berks

I S L LOUDON

SIR,—Dr Donaldson oversimplifies the problem of telling patients about their illnesses when he says “ someone ” should tell “ every patient ” before leaving hospital what is wrong with them He is dogmatic in implying that this is necessarily an important part of their treatment, and, I suggest, misguided if, in this context, he agrees with Emerson that “ knowledge is the antidote to fear ”

Like many housemen, I have been that “ somebody ” for a year now I regard explanation to patients as, in large part, the houseman’s responsibility and have tried conscientiously to deal with the problem, but I don’t think I have evolved any satisfactory method

Even with non-malignant disease it is far from easy While agreeing with Dr Donaldson that, too often, a patient is given inadequate information, it is remarkably difficult to explain to a layman anything except the simplest of diseases On many occasions the consultant, the registrar, and I have given careful explanations to patients, only to find by the questions asked later that virtually nothing has been grasped of what has been said

Malignant disease presents an even more difficult problem Some patients undoubtedly wish to know what is wrong with them no matter what the implication Personally, I think this a comparatively small proportion, but they should be told Others show by their discussion both with doctors and nurses, or by their avoidance of discussion, or refusal to face up to manifest evidence of physical deterioration, that they do not want to be told anything I have seen the personalities of such patients disintegrate at having unwanted explanation thrust upon them Others purport to want to know, but, by the way they word their questions, do not want the truth How else can one interpret the question “ I haven’t got cancer, have I doctor ? ” Is the correct reply to this “ yes ”—however circumlocuted ? It is simply not true, in my experience, that “ very seldom will a ‘ white lie ’ have to be told ” to a patient It is necessary quite often

Telling patients about their illnesses is not something that can be managed by any rule-of-thumb Human beings must be judged individually According to the ability of the doctor to do this astutely, so will he be able to decide on the form of explanation suited to each patient

London, W 1

SIDNEY CROWN

DRUG DOSAGE FOR INFANTS

SIR,—Your annotation of Oct 29 drew attention to a formula based on surface-area The method, which involved the calculation of the 0 7 power of the weight in kilogrammes, was said to be “ both convenient and accurate ” Before we all rush for logarithm tables and slide-rules, it would be as well to examine these claims

The convenience of a method is always a matter of opinion I venture to suggest that the use of a nomogram has much to commend it (Incidentally, poor mathematician that I am, to my humble reckoning (kg)$^{0\ -}$ consistently comes out to 10 times the right figure As regards accuracy, this raises several important issues What degree of accuracy is necessary when prescribing for children ? Is the danger one of giving too much or too little ? Does it matter, for instance, if a child with a surface area of 0 4 m^2 (18 lb) is administered the dose appropriate for a 0 5 m^2 (24 lb) ? Ought we to correct for the fact that average household teaspoon holds 1 ml more than the apothecary's ? Should we insist that amounts left on the spoon, in the glass, and down the bib are accurately measured and replaced ?

Most pædiatricians will concede that such accuracy is unnecessary Children have a generous margin of tolerance to drugs Most three-year-olds tolerate, and indeed need, adult doses (e g , antibiotics, anti-histamines, steroids, vitamins) and some require even more A six-year-old 0 8 m^2 enuretic may sleep heavily on 20 mg of amphetamine, whereas the average adult lies awake on a quarter of this dose The 0 25 m^2 baby and the 2 5 m adult are sedated by the same dose of phenobarbitone Even with drugs to which infants are particularly susceptible (e g , morphine, aspirin, iron) a 20% error either way will probably have little ill-effect

There can be no substitute for experience in prescribing an effective and safe dose of a particular drug for a particular child with a particular disease Much as I condemn formulæ for this purpose, my solution to the problem of the new or doubtful drug is to regard the adult dose appropriate for 100 lb and to extrapolate accordingly—a method which shows surprising approximation to the surface-area scale and engenders the comfortable feeling that the amount administered will be safe if not effective

Students are still taught one or more of the many formulæ devised for the calculation of drug dosage for infants and children Their multiplicity is good evidence that none is satisfactory The addition of yet another formula cannot detract from the wide variations of children in their reaction to drugs as compared with adults The only answer is never to be far from a comprehensive set of dosage tables There can be no such thing as a satisfactory formula

London, S E 1 HERBERT BARRIE

CANCER OF THE ŒSOPHAGUS

SIR,—I was interested in the article by Mr Greening and Mr Ramsay (Nov 19), and I should like to support their contention that an indwelling tube left in the œsophagus to traverse a malignant structure, in inoperable cases, should be of the largest possible bore so that the patient can swallow semi-solid food rather than fluids only

I cannot help thinking, however, that the tube and apparatus which they described, and illustrated, is unnecessarily complicated, when there is, in general use, the excellent Mousseau-Barbin tube which fulfils all their requirements Furthermore, the fact that this tube is too large to go through the œsophagoscope does not mean that it cannot be inserted through the mouth, and I should like to describe the method which, of late, I have found to be simple and effective

An œsophagoscope is passed, under general anæsthetic, and the site of the growth is noted accurately and the stricture dilated with bougies to the maximum size A fairly small gum-elastic bougie, say size 8, is than passed through the stricture and left in position while the œsophagoscope is withdrawn A Mousseau-Barbin tube is then cut short at such a point that when the funnel-shaped upper end is engaging with the top of the growth it is known that the cut lower end will be in the stomach (easily assessed with the knowledge of the site of the growth) The cut end should be clean and smooth This prepared tube is then threaded over the inlying bougie and pushed down into the hypopharynx with the finger A small œsophagoscope is then threaded over the bougie until its lower end engages within the funnel end of the tube One then merely pushes the tube down with the œsophagoscope, and it is guided through the previously dilated stricture along the *indwelling bougie* When the appropriate distance has been reached—and this can be read off on the graduations on the œsophagoscope—the instrument and the bougie are removed, leaving the Mousseau-Barbin tube in position

Patients who cannot be treated this way are those in whom it is impossible to find a way through the growth with the initial bougie As a rule this difficulty is only met when the growth is at the lower end of the œsophagus or the cardia, and in my experience a lot of these growths require an exploratory thoracotomy to demonstrate inoperability, and the tube can be inserted via a gastrostomy on these occasions

Park Hospital,
Davyhulme Urmston
Manchester JOHN DARK

POSTPARTUM PRE-ECLAMPSIA

SIR,—I read with interest the article by Flight-Lieutenant McFadyen (Nov 5) and Mr Sophian's comments (Nov 12) It is unfortunate that no description of the placenta was included, for I believe the placenta is the key to the cause of postpartum pre-eclampsia

Separation of an infarcted placenta is likely to be less complete than that of a healthy placenta, because fragments of the fresh friable infarcts tend to break off Unlike healthy placental tissue or membranes, whose retention in the uterus causes hæmorrhage or sepsis, red infarcts are partly proteolysed and so comparatively absorbable When absorbed into the maternal circulation they constitute " foreign " stress-producing material, which is nephrotoxic and causes toxæmia—albuminuria, oliguria, renal ischæmia, and hypertension—or accentuates existing toxæmia, or leads to a recrudescence of toxæmia some days after the death of a fœtus retained in utero The rate of their absorption depends on the pumping action of uterine contractions, and the *intensity* of the toxæmia that results is proportional to the uterine activity (and also to the quantity and condition of the infarct material retained in utero)

This explanation offers a different interpretation, but conforms with the statement of Mr Sophian that " the contracting postpartum uterus provokes renal ischæmia " The contracting intrapartum uterus also does so Ergometrine, too, increases uterine activity, accelerates absorption, and (as Flight-Lieutenant McFadyen mentioned) aggravates the toxæmia The great increase in maternal cortocosteroids, correctly stated by Mr Sophian to be a non-essential part of the pre-eclamptic reaction, is probably provoked by the entry of " foreign " placental products during and after labour, when the uterus is most active The coexistence of red infarcts and albuminuria was observed many years ago by Young,[1] and absorption from them of nephrotoxic material seems a more reasonable explanation of toxæmia than uterine stretch

Thus, although the incidence of eclampsia reaches its peak during the hours of labour (fully 30%, of cases occurring then) when stretch and activity of the uterus are both at their height, severe toxæmia or eclampsia may accompany the birth of a small, very premature baby—when the uterus is active but has been little stretched—or it may follow the birth of a baby by fully a day or two, when the uterus is still active but has ceased to be tensely stretched

Inability to explain postpartum toxæmia and eclampsia has been a major obstacle to the acceptance of previous theories about the cause of eclampsia Various workers have named various factors as specific causes My own nominee is trans-placental hormones,[2] but I believe these are only one important factor Toxæmia results from the interplay of various factors—extrinsic (diet), intrinsic (hypertensive, renal), hormonal, mechanical, and infective—which lead to vasospasm and infarction I have described[3] the pre-infarct and post-infarct stages of toxæmia, and postpartum pre-eclampsia is, I believe, a normal part of the latter stage

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[1] Young J Proc R Soc Med 1914 7 307

Reading K D SALZMANN

TUBERCULOSIS NOTIFICATION

SIR,—You quote (Nov 5, p 1036) from the Registrar General's commentary the official figure for tuberculosis notifications in 1949 as 50,000 and for 1958 as 30,000

On paper this looks very good and in fact would be good if 1958 were a true figure You have previously published from me evidence that when the number of attested (tuberculin-tested) cattle increased, human tuberculosis also increased, and this applies to both pulmonary and non-pulmonary tuberculosis

On Oct 1 this year the whole of Great Britain was declared free of cattle tuberculosis so that during 1949–58 eradication of cattle tuberculosis was in its final stages

Also during this period I suspect that the official figure was not correct I remember a report from Hampshire of pulmonary and non-pulmonary tuberculosis in the same house neither case had been officially notified I suggest these are not isolated cases

My opportunity of finding such evidence in a smallish veterinary practice is limited, but I will hazard that if all the individuals with tuberculosis were enumerated the 30,000 would be very near 100,000

High Wycombe, Bucks L PITCHER

WORKING WIVES—AND THEIR CHILDREN

SIR,—I have almost completed a review of the subsequent careers of the Oxford women medical graduates, and the findings are somewhat disturbing 75 of the 93 women, who graduated between 1941 and 1950, have married Of these 75 married women, 32 (43%) are practising between half and full time, 15 (20%) are practising less, and usually much less than half-time and the majority of these are anxious to spend more time in medicine, 6 (8%) are not practising and have no desire to resume, while 22 (29%) are not practising but are very anxious so to do on a part-time basis

Accordingly about half of these married women seek, but are unable, to continue the career for which they trained It would take too long to set out all the factors which cause this situation, and although it is true that lack of domestic help, income-tax laws, and the husband's occupation all play their part, yet the principal factor is the unwillingness of hospital authorities, medical officers of health, and general practitioners, to accept women in half-time posts Unless the Ministry of Health can induce a change of heart on this point, it would be wiser, from the point of view of the nation's economy, if the admission of women to medicine were severely restricted, as the male wastage is so much less On the other hand, they arrange things better in many European countries, where married medical women have no difficulty in obtaining satisfactory posts on a part-time basis

The situation with regard to those who graduated prior to 1940 is rather different as a far higher proportion have remained single, for as one of them wrote " my generation of medical women were brought up neither to receive nor expect to receive any special consideration because we were women The present generation takes it for granted that medical practice can be arranged around the life domestic "

My advice, based on this study, to the woman medical student who wished to combine medical practice and matrimony would be a variant of that given by the oracle of Bouverie Street, " Don't get married until you have established yourself in medicine, marry a doctor and obtain long leave, but don't resign your post while having a baby, and thereafter only work half to three-quarters time, alternatively go abroad to a country (there are several) where domestic help is plentiful " But Cupid is notoriously deaf to sage advice

The Radcliffe Infirmary,
Oxford A H T ROBB-SMITH

MODERN CLINICAL BIOCHEMISTRY

SIR,—As head of a department which produces biochemists I should like to comment on the recent letters by Dr Hendry (Oct 29, Nov 19), Dr Woolf (Nov 12), and others

At the present time the demand for biochemists with science degrees greatly exceeds the supply Of the various possible sources of employment the National Health Service offers a reasonably good financial inducement to the young scientist, but in my experience it is exceedingly difficult to persuade science graduates to accept posts in hospital biochemical laboratories One of the things which deters them from entering the hospital service is the feeling that they will be regarded by their medical colleagues not as professional scientists and university graduates but rather as subordinates in the intellectual, economic, social, and professional category of technicians and medical auxiliaries That these fears are not without justification is very beautifully illustrated in the unfortunate letter of Dr Osborn (Nov 5) It is true that science graduates express fewer misgivings about entering the biochemical laboratory of a large teaching hospital where they are under the control of a professional biochemist as head of a department, but it is becoming increasingly difficult to persuade them to work in the smaller hospitals where all the laboratory services are grouped under a non-biochemical pathologist

One disturbing result of this attitude is that the best science graduates tend to shun hospital employment—it is very rare for a first-class honours man to enter a hospital laboratory The consequent flow of a number of the less able graduates to the hospitals is apt to give the medical staff a less favourable impression of the usefulness of scientists in their midst than they might otherwise gain And so the vicious cycle begins

There is no doubt that the best training for a hospital biochemist is an honours science degree in biochemistry supplemented by a medical qualification, but such a training is lengthy and only a few students (about two per year in Glasgow) are willing to face it The basis of the biochemist's training must be *chemical* whereas that of the pathologist must be *medical*, but the biochemist at the end of his training must be able to discuss problems of mutual interest for the patient's welfare with his pathological colleagues as an equal and not as a subordinate and he must have direct access to the clinician in charge of the patient This is not merely a matter of professional pride—it is the only way to encourage the ablest biochemists to enter, and to remain in, hospital work

It may be administratively untidy to have the biochemical laboratory of a hospital separate from the pathological laboratory which covers morbid anatomy, bacteriology, and hæmatology, but it is becoming more and more obvious that such an arrangement is essential for the good of the patient in any large up-to-date hospital which expects good service from a competent staff In those hospitals where this system operates, the results amply reveal its justification

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[2] Salzmann, K D *Lancet*, 1955 ii 953

[3] Salzmann K D Aetiology and Arrest of Pre-eclamptic Toxæmia with Early Ambulant Treatment London 1960

Department of Biochemistry,
University of Glasgow — J N Davidson

HYALINE MEMBRANE FOLLOWING TOTAL BODY RADIATION

Sir,—According to the preliminary communication in *The Lancet* of Nov 5, patients with far-advanced malignancies have been subjected to total body irradiation for an experimental purpose, and one not related to their disease

The effects of such irradiation are severe, and, at the dosage mentioned, lethal

I think these circumstances ought to be remarked, particularly as you ignore them in your editorial comment

Manchester — J L Dobbie

*** We showed Dr Dobbie's letter to Captain King and his colleagues and their reply follows —Ed L

Sir,—We should like to make the following points and perhaps clear up this misunderstanding

(1) Except for one (who had a kidney transplant) all patients selected for this form of therapy had disseminated malignancies Conventional therapy had failed in these patients and localised radiation therapy revealed some degree of radiosensitivity

(2) The observations on human lung were incidental to and not the purpose of the therapy

(3) As you will note, the operative mechanisms of plasmin inhibition following total body radiation were worked out in dogs, not humans

(4) As a result of extensive investigations on the subject of total body radiation in animals, the serious effects in the unsupported subject are well appreciated at the National Naval Medical Center, Bethesda

(5) The efficacy of total body radiation will be presented in detail in a future publication

William H Fleming
Jeno E Szakacs
Thomas C Hartney
E R King

U S Naval Hospital,
Bethesda, Maryland

SUICIDE

Sir,—The changes in the law of suicide foreshadowed by a report from the Criminal Law Revision Committee[1] will be welcomed by doctors, magistrates, and police officers alike It has long been recognised that the existing law has no deterrent effect and creates a great deal of distress Frequently it makes treatment more difficult by causing patients to deny suicidal intentions for fear of prosecution Bringing a person who has attempted suicide before a court and placing him on probation under the condition that he receives psychiatric treatment is quite unnecessary There is no reason whatever why England alone of all countries in the world should require special legal provisions, outside the mental-health legislation, to make people in distress accept medical and social help As Dr Casson (Nov 5) referred to my studies on attempted suicide, or rather to a brief second-hand report of my studies, I wish to state that my observations[2] [3] lend strong support to those who have for a long time advocated the abolition of the existing law Its background and its effects were fully discussed three years ago[4] On that occasion Batchelor reported on the way the problem is dealt with in Scotland where suicide and attempted suicide are not criminal offences

Dr Ahrenfeldt's letter (Nov 19) about the attitude of the Church to suicide contains no reference to the recent report by a committee set up at the suggestion of the Archbishop of Canterbury for the purpose of examining the law of suicide[5] The first of the four recommendations made by this committee was that attempted suicide should cease to be a criminal offence

The University,
Sheffield — E Stengel

CIGARETTES IN HOSPITALS

Sir,—Some hospitals issue pamphlets about the risks of cigarette smoking, and many of their doctors, even if they can't stop the habit themselves, advise patients not to start Is it not time that these hospitals reversed their illogical decisions to provide cigarette vending machines?

Enfield,
Middlesex — C Allan Birch

ADMINISTRATION IN MENTAL HOSPITALS

Sir,—The Mental Health Act makes it quite clear that the responsible medical officer is not responsible or answerable for the patient's treatment to any other doctor Therefore, in answer to Dr Falla (Nov 12), I would say that I do not need to know anything about those patients which are not directly under my personal care Hypothetical cases make bad laws, but it follows from what has been said that, as medical superintendent, I would know nothing about the aggressive psychopath mentioned, and therefore the consultant, and he alone, would be called upon to give an explanation of the action of his patient

I would, indeed, say that treatment includes control of freedom, prescription of social and occupational activities, the amount of pocket-money that a patient is allowed, and many other similar things, but that the actual *prescription of these* things will vary from patient to patient according to the judgment of the responsible medical officer Nevertheless the medical superintendent being responsible for the efficiency of the whole hospital, and not only for the efficiency of his own team, has to see that these things are available for " prescription " Also he is responsible for coordinating and controlling new ideas and requests coming from the teams so that chaos does not ensue It is also his job to see that all suggestions for improvement in the clothing of patients, the standard of catering, furnishing, and architectural improvement, lengthening of visiting hours, or anything else that is agreed upon at the weekly senior-staff meetings are carried out for the benefit of all the teams All the new ideas coming out of the senior-staff meeting will then be put into practice satisfactorily throughout the hospital and implemented after any necessary consultation between the medical superintendent, chief male nurse, matron, and hospital secretary

I think this really answers Dr Bardon (Nov 12), for it will be seen that a medical superintendent responsible for the efficiency of the whole hospital does not in anyway impair the freedom of the clinical teams In any event, Dr Bardon has misread the Act The Act has nothing to say, either specifically or implicitly about how a hospital is adminstered His idea of an elected chairman might well work and become the pattern of the future, as I suggested in my first letter But in my view most mental hospitals at present still need a medical superintendent who directs the hospital as a whole and who has powers, not to interfere in any way with the treatment of a patient, but to interfere in matters of administration and discipline of medical and nursing staff if, in his opinion, their action might be seriously detrimental to the harmony of the hospital For such decisions he should be answerable to the hospital management committee or the regional hospital board who appoint him and not to his colleagues

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[1] Criminal Law Revision Committee second *report (Suicide)* H M Stationery Office, 1960 See *Lancet* Oct 29 1960 p 976

[2] Stengel, E, Cook N G Attempted Suicide London, 1958

[3] Stengel, E *Medico-legal J* 1959 27 114

[4] *Proc R Soc Med* 1958 51, 297

[5] Ought Suicide to Be a Crime? Church Information Office Westminster, 1959

Evolution is much better than revolution and my feeling is that Dr Bardon and many clinical psychiatrists express their views so radically and so forcibly that I suspect that powerful unconscious motives may be at work. Finally we should not slavishly follow the general-hospital pattern of administration It too has its faults.

The Towers Hospital
Humberstone, Leicester

H B KIDD

PROGNOSIS AND ANTICOAGULANT PROPHYLAXIS AFTER CORONARY OCCLUSION

SIR,—Like Dr Byron Evans (Nov 26), many of us are grateful to Professor McMichael and Dr Parry (Nov 5) for questioning the value of long-term anticoagulant prophylaxis after cardiac infarction It is dangerous, and cannot but be tedious except for a hypochondriac

It would be a pity, however, if there were a premature reaction, provoked by annoyance with opinionated but inadequately informed patients, against its use in the first few weeks after an infarction. Many observers believe its use in this period to be vitally important

We are thankful for iconoclasts like Dr Byron Evans If too inflexible, however, they are in danger of getting cut off by the tide of progress

Barton-on-Humber,
Lincs

S H F HOWARD

SHINGLES AND CHICKENPOX

SIR,—I think the following case shows that the relationship between these conditions is not necessarily indirect, as Dr Ball (Nov 19) suggests, and that an intermediate host may not be required

A young woman was admitted under my care in 1955 to the British Military Hospital at Rinteln, B.A.O R , with herpes zoster of the ophthalmic division of the left trigeminal nerve, causing severe conjunctivitis and keratitis Because her husband was away on a military exercise, she was admitted with her infant aged six months Fourteen days later, the baby developed chickenpox, and I think it reasonable to assume that contact here was direct, since they were nursed in an isolation ward.

Military Hospital
Colchester

H FOSTER.

RESPIRATORY OBSTRUCTION DUE TO FAULTY ENDOTRACHEAL TUBE

SIR,—I was interested to read the article of Oct 1 by Dr Pryer and his colleagues I have twice encountered the accident they describe, and I think it is important that it should be mentioned in the textbooks The story in the two instances I mention was the same—a sudden onset of complete obstruction in a previously uneventful anæsthetic. Fortunately in both cases I was called before a fatal outcome, and by deflating the cuff completely, relieved the situation When the tubes were examined subsequently, it was found that there was a " hernia " in the cuff on the side opposite the side of the bevel

When I am teaching I always include this among the complications of endotracheal intubation I think that too small a tube, and overinflation of the cuff are the precipitating causes, and if the tube is appropriately chosen and the cuff just adequately inflated, this accident should not occur

Brisbane Hospital
Brisbane.

RUTH MOLPHY

CHEST X-RAYS AND RADIATION HAZARDS

SIR,—I write in complete agreement with Dr Beresford's letter of Nov 26 I should like to enlarge upon his condemnation of fluoroscopy sessions as a means of diagnosing early pulmonary tuberculosis This method is still adopted at certain clinics in preference to a chest X-ray I have long felt that fluoroscopy for this purpose is entirely unjustified, not only, as Dr Beresford points out, because the amount of radiation at each examination is substantially greater than the controlled dose given by radiography, but because there is no permanent record which could be of great assistance later Furthermore, I have tested the method myself by screening a few patients whose chest X-rays showed a minimal tuberculous lesion and found that, even after adequate accommodation to the darkness (my day and night vision is perfect), I was quite unable to detect these lesions on fluoroscopy And, of course, I did know where to look, having first seen the chest X-ray

Bow Arrow Hospital,
Dartford.

M O J GIBSON

HYPERSENSITIVITY TO MILK AND SUDDEN DEATH IN INFANCY

SIR,—The team of workers who have produced, in your issue of Nov 19, such a convincing solution to the mystery of sudden cot-death in infants are to be congratulated That these tragic deaths may result from the aspiration of cow's milk during sleep in a child who is already sensitised to the protein in the milk is, as they emphasise, a valid reason for encouraging breast-feeding wherever possible Those of us who still believe that breast milk is the only proper food for the healthy baby will be glad to have such strong support for our beliefs at a time when so much is written in defence of artificial feeding

Inevitably there will be occasions when breast-feeding is impossible, and then we must be especially careful to guard against the danger of aspiration of feeds

In the past, in my opinion, far too much stress has been put upon the dangers of suffocation. This is perhaps the reason why the nursing of infants in the prone or semi-prone position has not been more widely practised Provided the baby lies upon a firm mattress *without* a pillow, his nose-clearing reflex ensures that his head is always turned to one side. Lying in this position regurgitation becomes almost impossible, and, if it should occur, the milk is possetted harmlessly upon the sheet.

Premature babies regurgitate more easily than full-term infants, and some experienced nurses have learned to overcome this tendency by nursing them in the prone position. And the radiologist can demonstrate that the one position in which the infant cannot regurgitate an opaque meal is semi-prone on his right side.

Incidentally, this is a much more effective way of posturing the infant with cardiochalasia or hiatus hernia, particularly if the infant is tilted by raising the head of the cot on 18-inch blocks

London, N.W.3

R. J K BROWN

SIR,—Using the guineapig, an animal well known to be peculiarly immunologically fragile, Dr Camps and his colleagues (Nov 19) have nevertheless demonstrated as close an analogous pathogenetic explanation of the " cot-death syndrome " in infants as we are ever likely to treatment under the National Health Service Mr POWELL In 1959, 1503 aliens were reported as entering, or attempting to enter, this country for medical treatment 6 of these were refused entry Steps were taken to ensure that the remainder paid for the treatment Mr EVANS Will the Minister assure the House that in this matter he will follow the policy of all those Ministers who have held office since the inception of the National Health Service scheme? Will he refrain from looking at this matter from a narrow nationalistic point of view or with the idea of making petty economies? Mr POWELL This thing is an abuse However relatively small the cost, it ought, so far as is practicable, to be prevented There has been no difference in policy in this matter since the original Act

Mr MICHAEL FOOT Is the Minister aware that when the service was first introduced the idea of giving treatment to sick foreigners was not regarded as an abuse but that we gloried in it? Mr POWELL There has never been any question of persons from abroad who fall sick in this country receiving attention under the National Health Service That has not been in question from either side of the House But it is not in accordance with the intention of the Act that aliens should come to this country for the purpose of getting treatment under the Act

Remploy and the Mentally Disordered

Lord STONHAM asked H M Government if, in areas where suitable facilities were available, it would be possible for Remploy to act as agents for local health authorities in discharge of their responsibilities under the Mental Health Act, to provide training and occupation for the mentally disordered —The Earl of DUNDEE, the Minister Without Portfolio, replied My Lords, Remploy already provide employment for a number of mentally disordered persons The company will continue to consider persons handicapped by mental disorders, together with other disabled persons for vacancies in Remploy factories, but it has no power to act as agents for local health authorities in the provision of training or occupation Lord STONHAM Is the noble Earl aware that my question invites consideration of granting such powers to Remploy? I would ask him to look at this matter again, particularly—having regard to the tremendous success of Remploy—with a view to seeing whether the Remploy sales organisation could not be used to dispose of the products of these centres, and in that way give the mentally disordered people a chance of earning at least part of their living instead of being in merely therapeutic centres The Earl of DUNDEE I am very grateful to the noble Lord for his appreciation of the excellent work which is being done by Remploy They do employ, out of a total of 6300, I think about 500 people who are suffering from various kinds of mental or nervous disorders, and in view of the possibility of some of the persons placed by local authorities in special centres being able to go to Remploy afterwards very close touch is maintained But that is not quite the same as giving the primary responsibility to Remploy for the care of mentally disordered people Lord STONHAM Is the noble Earl aware that what I have in mind is that in these local authority centres mentally disordered people will make something and it is absolutely essential that it should be sold by a skilled organisation, otherwise they will be at the mercy of charitable disposals and it will not be a really serious project Would he consider that possibility? The Earl of DUNDEE I gather the noble Lord is thinking of more efficient arrangements for the sale of their products, and I will most certainly look into that

Poliomyelitis Vaccination

Poliomyelitis vaccine is now sufficiently plentiful to permit vaccination of those aged 40 and over who are not covered by the existing arrangements From Jan 1, family doctors will be able to vaccinate any such person who, they consider, requires this protection

Children Remanded to Prison

During the nine months ended Sept 30, 1960, in England and Wales, 585 boys and 23 girls under seventeen years were remanded to prison instead of being sent to remand homes

Obituary

WALTER WEIR GALBRAITH

M B Glasg, F R F P S, F R C S E

Mr Walter Galbraith, consulting surgeon to the Western Infirmary, Glasgow, and a former president of the Royal Faculty of Physicians and Surgeons of Glasgow, died on Nov 25 at the age of 71

Born in Glasgow, he was the eldest son of the late W B Galbraith, J P, C A, and a brother of Lord Strathclyde He was educated at Glasgow Academy and the Leys School, Cambridge In 1914 he graduated M B from the University of Glasgow, and during the 1914-18 war he served overseas as a surgical specialist

On demobilisation he was appointed to the staff of the Western Infirmary in Glasgow and rapidly earned a reputation as a gifted and courageous general surgeon He early found his special interest in urology, and he was largely responsible for setting up a department of urology in the Western Infirmary

He was also active in the affairs of his profession, his specialty, and his medical school In 1949 he was president of the British Association of Urological Surgeons, and the following year he became president of the Royal Faculty of Physicians and Surgeons of Glasgow At the time of his death he was a vice-president of the Royal College of Surgeons of Edinburgh He was a member of the Scottish Health Services Council and for many years represented the Royal Faculty on the Joint Consultants' Committee and on the medical Whitley Council

When he retired from practice in 1954 he made his home near Troon There he found much pleasure in gardening and in the sports in which he excelled—golf, fishing, and shooting Yet he accepted his leisure as an opportunity for further service He continued as a member of the Joint Consultants' Committee, as a governor of Glasgow Academy, and as a director of the McAlpin Nursing Home, and he accepted two new charges in membership of the Western Regional Hospital Board and of the court of Glasgow University

A B K writes

"Under Walter Galbraith's leadership the department of urology at the Western Infirmary made many contributions to the advance of surgery Yet he will be remembered perhaps more for his generous personality which did so much to foster a happy relationship among the urological departments in the city No visitor to his department was allowed to leave without being pressed to see the work of the others He travelled extensively at home and abroad with urologists and with general surgeons He revelled in companionship His friendly interest strengthened many a younger man His blunt but kindly criticism stimulated many a contemporary His opinions were often based on emotion rather than on regulations They were valued for their sincerity and humanity To everything which he did he brought an unsurpassed gift for fellowship He will be mourned by an innumerable company of friends"

S A pays tribute to him as a Scot as well as a surgeon

"Walter's shrill and arresting 'What?' was like a pistol shot It was the opening snap of cerebration By the time the startled and discomfited colleague had filled diastole with a twice-told tale, Walter had formed an opinion—and a shrewd one at that This idiosyncrasy epitomised much of his character Essentially he was a man of business, a man of affairs, but schooled in the discipline of surgery, and in his chosen craft he was a master His outward cheerfulness and boisterous bonhomie were perhaps acquired in the interests of his friends Behind this carefree style there was the astute brain of the relentless Scot—vigorous by disposition, yet able to carry the chains of convention and caution with relish rather than with dismay The technical precision of the surgical specialist was complementary to the assiduousness of the committee-man Purposive, tireless, and intensely patriotic, Scotland was his eyrie—and there he brooded like a golden eagle, jealously maintaining and defending the prestige of medicine in a changing world "

Mr Galbraith is survived by his wife, a son, and two daughters

Public Health

Foot-and-mouth Disease

THE present outbreak of foot-and-mouth disease [1] continues to spread despite all precautions At midnight on Friday, Nov 25, the Ministry of Agriculture announced that the movement of farm animals and the holding of markets was restricted in all counties of England north of a line from Bristol to London, with the exception of Cumberland and Westmorland This widespread restriction was imposed because, during Friday, foot-and-mouth had been confirmed in Nottinghamshire, Essex, and Shropshire, and the outbreaks there could not be connected with any of the earlier cases

By Monday, Nov 28, a 9th case of foot-and-mouth disease had been confirmed in the Orkneys, bringing the number of outbreaks in Scotland to 66 The United Kingdom total was then 193 3 more cases were confirmed during the day

So far, the disease has not spread to Eire, but the Department of Agriculture in Dublin has asked farmers, cattle-buyers, and others who have any contact with livestock or meat in Britain not to visit Ireland until the present crisis is over

There will be no livestock at this year's Smithfield Show, for the first time since 1798

Up to Nov 28, 14,700 cattle, 16,750 sheep, 6700 pigs, and 25 goats had been slaughtered

Industrial Biological Research Association

A new research organisation—the British Industrial Biological Research Association—has been formed to study the possible effects on health, and to ensure the harmlessness, of substances which may be ingested in food, drink, and cosmetics Supported by several leading companies, it is welcomed by interested Government departments and will receive a grant from the Department of Scientific and Industrial Research

The Association's main object is the establishment of a biological research station for investigating the effect of substances used in food manufacture, either as processing aids for or flavouring and colouring food, as well as those which may get into food from pesticides, from plant used in food manufacture, from packaging materials, or from utensils The Association hopes to build its laboratories at Leatherhead, Surrey, on land leased from the British Food Manufacturing Industries Research Association, which has offered to share some facilities and administrative services in the initial stages The temporary headquarters of the Association are at 11, Green Street, London, W 1

Classification of Occupations

Classification of Occupations [2] has been compiled by the General Register Office, England and Wales, and the General Registry Office, Scotland, primarily for use in the Census on April 23, 1961 It is also being used by the Registrars General for coding occupations stated at the registration of deaths and in morbidity surveys and inquiries The *Classification* is published in the hope that it will be of interest to research-workers who may wish to relate their results to the Census statistics

Diary of the Week

DEC 4 TO 10

Sunday, 4th

Institute of Laryngology and Otology 330, Gray s Inn Road, W C 1
10 15 A M Mr Wallace Black Common Ear, Nose, and Throat Conditions

Monday, 5th

University College London, Gower Street, W C 1
5 30 P M Prof W S Feldberg Mediators of Allergic Reactions
Postgraduate Medical School of London, Ducane Road, W 12
4 P M Dr J F Goodwin Effect of Drugs on the Pulmonary Circulation

Tuesday, 6th

Royal Society of Medicine, 1, Wimpole Street, W 1
5 30 P M *Pathology* Prof N F Maclagan Changing Views on Jaundice (Presidential address)
8 30 P M *Orthopædics* Mr Walpole Lewin, Mr R C Connolly, Prof Roland Barnes, Mr F C Durbin Injuries of the Head and Neck
British Postgraduate Medical Federation
5 30 P M (London School of Hygiene and Tropical Medicine, Keppel Street, W C 1) Prof D G Catcheside Functional Structure of Genes
Institute of Obstetrics and Gynaecology
3 P M (Hammersmith Hospital, Ducane Road, W 12) Mr J A Stallworthy Carcinoma of the Uterus
St Mary s Hospital Medical School, W 2
5 P M (Wright-Fleming Institute) Mr Aleck Bourne Some of My Mistakes
West End Hospital for Neurology and Neurosurgery, 91, Dean Street, W 1
5 30 P M Mr K I Nissen Orthopædic Surgery of Spastic States
Royal Army Medical College, Millbank, S W 1
5 P M Prof F A R Stammers Pain in the Arm
Research Defence Society
5 30 P M (University College London, Gower Street, W C 1) Prof J H Burn Testing Drugs on Man (Stephen Paget lecture)
Leeds Neurological Sciences Colloquium
5 15 P M (General Infirmary at Leeds) Dr Eliot Slater Schizophrenic-like Psychoses of Epilepsy

Wednesday, 7th

Royal College of Surgeons of England, Lincoln s Inn Fields, W C 2
2 30 P M Sir Stanford Cade Malignant Melanoma (Bradshaw lecture)
Royal Society of Medicine
5 15 P M *History of Medicine* Mr Dickson Wright History of Opium
8 P M *Surgery* Mr G A Mason, Mr Charles Drew, Mr A J Cokkinis, Mr G E Mavor Coronary and Mesenteric Vascular Occlusion
Postgraduate Medical School of London
2 P M Dr A E Kellie Steroid Assays
Institute of Dermatology, Lisle Street, W C 2
5 30 P M Dr R W Riddell Yeasts as Pathogens
Institute of Diseases of the Chest, Brompton, S W 3
5 P M Mr Matthias Paneth Surgery of Secundum Defects of the Atrial Septum
Institute of Obstetrics and Gynaecology
2 P M (Queen Charlotte s Hospital, Goldhawk Road, W 6) Mr G B Gibson Postmaturity
Royal Institute of Public Health and Hygiene, 28, Portland Place, W 1
3 30 P M Dr Kenneth Soddy World Mental Health Year—International Trends in Mental Health Work
Midland Medical Society
8 30 P M (Birmingham Medical Institute, 36, Harborne Road, Birmingham, 15) Dr R Bodley Scott Acute Leukæmia—the Present Therapeutic Position

Thursday, 8th

Royal College of Physicians of London, Pall Mall East, S W 1
3 P M Sir George Clark Thomas Linacre (Commemoration of the Quincentenary of Linacre s birth)
Royal College of Surgeons of England
5 P M Mr H J Seddon Manchester Ship Canal and Colonial Frontier (Robert Jones lecture)
University College London
5 30 P M Sir Solly Zuckerman Social Function of Science—1960 (Rickman Godlee lecture)
British Postgraduate Medical Federation
5 30 P M (London School of Hygiene and Tropical Medicine) Dr E J L Lowbury Drug Resistance and the Response to Chemotherapy
Institute of Dermatology
5 30 P M Dr P F Borrie Disorders of Function in Cutaneous Blood Vessels and Lymphatics
Institute of Obstetrics and Gynæcology
4 30 P M (Chelsea Hospital for Women, Dovehouse Street, S W 3) Miss J A M Moore Dysmenorrhœa
Royal Society of Tropical Medicine and Hygiene, 26, Portland Place, W 1
7 30 P M Dr S Stott Dr E van Oye, Dr Henry Foy Hookworm Diseases
Alfred Adler Medical Society
8 P M (11, Chandos Street W 1) Dr Wilfred Barlow Anxiety and Muscle Tension
Honyman Gillespie Lecture
5 P M (University New Buildings, Teviot Place Edinburgh) Prof M L Rosenheim Small Kidney

Friday, 9th

Postgraduate Medical School of London
10 A M Dr Victor Wynn Metabolic Care of the Surgical Patient
4 P M Dr John Badenoch Malabsorption Syndromes
Institute of Laryngology and Otology
3 30 P M Dr Norman Hulbert Headache and Facial Pain

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[1] See *Lancet* Nov 26 1960 p 1183

[2] Classification of Occupations 1960 H M Stationery Office Pp 136 27s 6d

logy, and hæmatology, but it is becoming more and more obvious that such an arrangement is essential for the good of the patient in any large up-to-date hospital which expects good service from a competent staff In those hospitals where this system operates, the results amply reveal its justification

Department of Biochemistry,
University of Glasgow

J N DAVIDSON

HYALINE MEMBRANE FOLLOWING TOTAL BODY RADIATION

SIR,—According to the preliminary communication in *The Lancet* of Nov 5, patients with far-advanced malignancies have been subjected to total body irradiation for an experimental purpose, and one not related to their disease

The effects of such irradiation are severe, and, at the dosage mentioned, lethal

I think these circumstances ought to be remarked, particularly as you ignore them in your editorial comment

Manchester

J L DOBBIE

*** We showed Dr Dobbie's letter to Captain King and his colleagues and their reply follows —ED L

SIR,—We should like to make the following points and perhaps clear up this misunderstanding

(1) Except for one (who had a kidney transplant) all patients selected for this form of therapy had disseminated malignancies Conventional therapy had failed in these patients and localised radiation therapy revealed some degree of radiosensitivity

(2) The observations on human lung were incidental to and not the purpose of the therapy

(3) As you will note, the operative mechanisms of plasmin inhibition following total body radiation were worked out in dogs, not humans

(4) As a result of extensive investigations on the subject of total body radiation in animals, the serious effects in the unsupported subject are well appreciated at the National Naval Medical Center, Bethesda

(5) The efficacy of total body radiation will be presented in detail in a future publication

WILLIAM H FLEMING
JENO E SZAKACS
THOMAS C HARTNEY
E R KING

U S Naval Hospital,
Bethesda, Maryland

SUICIDE

SIR,—The changes in the law of suicide foreshadowed by a report from the Criminal Law Revision Committee [1] will be welcomed by doctors, magistrates, and police officers alike It has long been recognised that the existing law has no deterrent effect and creates a great deal of distress Frequently it makes treatment more difficult by causing patients to deny suicidal intentions for fear of prosecution Bringing a person who has attempted suicide before a court and placing him on probation under the condition that he receives psychiatric treatment is quite unnecessary There is no reason whatever why England alone of all countries in the world should require special legal provisions, outside the mental-health legislation, to make people in distress accept medical and social help As Dr Casson (Nov 5) referred to my studies on attempted suicide, or rather to a brief second-hand report of my studies, I wish to state that my observations [2, 3] lend strong support to those who have for a long time advocated the abolition of the existing law Its background and its effects were fully discussed three years ago [4] On that occasion Batchelor reported on the way the problem is dealt with in Scotland where suicide and attempted suicide are not criminal offences

Dr Ahrenfeldt's letter (Nov 19) about the attitude of the Church to suicide contains no reference to the recent report by a committee set up at the suggestion of the Archbishop of Canterbury for the purpose of examining the law of suicide [5] The first of the four recommendations made by this committee was that attempted suicide should cease to be a criminal offence

The University,
Sheffield

E STENGEL

CIGARETTES IN HOSPITALS

SIR,—Some hospitals issue pamphlets about the risks of cigarette smoking, and many of their doctors, even if they can't stop the habit themselves, advise patients not to start Is it not time that these hospitals reversed their illogical decisions to provide cigarette vending machines?

Enfield,
Middlesex

C ALLAN BIRCH

ADMINISTRATION IN MENTAL HOSPITALS

SIR,—The Mental Health Act makes it quite clear that the responsible medical officer is not responsible or answerable for the patient's treatment to any other doctor Therefore, in answer to Dr Falla (Nov 12), I would say that I do not need to know anything about those patients which are not directly under my personal care Hypothetical cases make bad laws, but it follows from what has been said that, as medical superintendent, I would know nothing about the aggressive psychopath mentioned, and therefore the consultant, and he alone, would be called upon to give an explanation of the action of his patient

I would, indeed, say that treatment includes control of freedom, prescription of social and occupational activities, the amount of pocket-money that a patient is allowed, and many other similar things, but that the actual prescription of these things will vary from patient to patient according to the judgment of the responsible medical officer Nevertheless the medical superintendent being responsible for the efficiency of the whole hospital, and not only for the efficiency of his own team, has to see that these things are available for "prescription" Also he is responsible for coordinating and controlling new ideas and requests coming from the teams so that chaos does not ensue It is also his job to see that all suggestions for improvement in the clothing of patients, the standard of catering, furnishing, and architectural improvement, lengthening of visiting hours, or anything else that is agreed upon at the weekly senior-staff meetings are carried out for the benefit of all the teams All the new ideas coming out of the senior-staff meeting will then be put into practice satisfactorily throughout the hospital and implemented after any necessary consultation between the medical superintendent, chief male nurse, matron, and hospital secretary

I think this really answers Dr Bardon (Nov 12), for it will be seen that a medical superintendent responsible for the efficiency of the whole hospital does not in anyway impair the freedom of the clinical teams In any event, Dr Bardon has misread the Act The Act has nothing to say, either specifically or implicitly about how a hospital is administered His idea of an elected chairman might well work and become the pattern of the future, as I suggested in my first letter But in my view most mental hospitals at present still need a medical superintendent who directs the hospital as a whole and who has powers, not to interfere in any way with the treatment of a patient, but to interfere in matters of administration and discipline of medical and nursing staff if, in his opinion, their action might be seriously detrimental to the harmony of the hospital. For such decisions he should be answerable to the hospital management committee or the regional hospital board who appoint him and not to his colleagues

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[1] Criminal Law Revision Committee second report (Suicide) H M Stationery Office 1960 See *Lancet* Oct 29, 1960 p 976

[2] Stengel, E., Cook N G Attempted Suicide London 1958

[3] Stengel E. *Medico-legal J* 1959 27 114

[4] *Proc R Soc Med* 1958, 51, 297

[5] Ought Suicide to Be a Crime? Church Information Office Westminster, 1959

Evolution is much better than revolution and my feeling is that Dr Bardon and many clinical psychiatrists express their views so radically and so forcibly that I suspect that powerful unconscious motives may be at work Finally we should not slavishly follow the general-hospital pattern of administration It too has its faults.

The Towers Hospital
Humberstone, Leicester
H B KIDD

PROGNOSIS AND ANTICOAGULANT PROPHYLAXIS AFTER CORONARY OCCLUSION

SIR,—Like Dr Byron Evans (Nov 26), many of us are grateful to Professor McMichael and Dr Parry (Nov 5) for questioning the value of long-term anticoagulant prophylaxis after cardiac infarction It is dangerous, and cannot but be tedious except for a hypochondriac

It would be a pity, however, if there were a premature reaction, provoked by annoyance with opinionated but inadequately informed patients, against its use in the first few weeks after an infarction. Many observers believe its use in this period to be vitally important

We are thankful for iconoclasts like Dr Byron Evans If too inflexible, however, they are in danger of getting cut off by the tide of progress

Barton-on-Humber,
Lincs
S H F HOWARD

SHINGLES AND CHICKENPOX

SIR,—I think the following case shows that the relationship between these conditions is not necessarily indirect, as Dr Ball (Nov 19) suggests, and that an intermediate host may not be required

A young woman was admitted under my care in 1955 to the British Military Hospital at Rinteln, B.A.O R, with herpes zoster of the ophthalmic division of the left trigeminal nerve, causing severe conjunctivitis and keratitis Because her husband was away on a military exercise, she was admitted with her infant aged six months Fourteen days later, the baby developed chickenpox, and I think it reasonable to assume that contact here was direct, since they were nursed in an isolation ward.

Military Hospital
Colchester
H FOSTER.

RESPIRATORY OBSTRUCTION DUE TO FAULTY ENDOTRACHEAL TUBE

SIR,—I was interested to read the article of Oct. 1 by Dr Pryer and his colleagues I have twice encountered the accident they describe, and I think it is important that it should be mentioned in the textbooks The story in the two instances I mention was the same—a sudden onset of complete obstruction in a previously uneventful anæsthetic Fortunately in both cases I was called before a fatal outcome, and by deflating the cuff completely, relieved the situation When the tubes were examined subsequently, it was found that there was a " hernia " in the cuff on the side opposite the side of the bevel

When I am teaching I always include this among the complications of endotracheal intubation I think that too small a tube, and overinflation of the cuff are the precipitating causes, and if the tube is appropriately chosen and the cuff just adequately inflated, this accident should not occur

Brisbane Hospital,
Brisbane.
RUTH MOLPHY

CHEST X-RAYS AND RADIATION HAZARDS

SIR,—I write in complete agreement with Dr Beresford's letter of Nov 26 I should like to enlarge upon his condemnation of fluoroscopy sessions as a means of diagnosing early pulmonary tuberculosis This method is still adopted at certain clinics in preference to a chest X-ray I have long felt that fluoroscopy for this purpose is entirely unjustified, not only, as Dr Beresford points out, because the amount of radiation at each examination is substantially greater than the controlled dose given by radiography, but because there is no permanent record which could be of great assistance later Furthermore, I have tested the method myself by screening a few patients whose chest X-rays showed a minimal tuberculous lesion and found that, even after adequate accommodation to the darkness (my day and night vision is perfect), I was quite unable to detect these lesions on fluoroscopy And, of course, I did know where to look, having first seen the chest X-ray

Bow Arrow Hospital,
Dartford
M O J GIBSON

HYPERSENSITIVITY TO MILK AND SUDDEN DEATH IN INFANCY

SIR,—The team of workers who have produced, in your issue of Nov 19, such a convincing solution to the mystery of sudden cot-death in infants are to be congratulated That these tragic deaths may result from the aspiration of cow's milk during sleep in a child who is already sensitised to the protein in the milk is, as they emphasise, a valid reason for encouraging breast-feeding wherever possible Those of us who still believe that breast milk is the only proper food for the healthy baby will be glad to have such strong support for our beliefs at a time when so much is written in defence of artificial feeding

Inevitably there will be occasions when breast-feeding is impossible, and then we must be especially careful to guard against the danger of aspiration of feeds

In the past, in my opinion, far too much stress has been put upon the dangers of suffocation. This is perhaps the reason why the nursing of infants in the prone or semi-prone position has not been more widely practised Provided the baby lies upon a firm mattress *without* a pillow, his nose-clearing reflex ensures that his head is always turned to one side. Lying in this position regurgitation becomes almost impossible, and, if it should occur, the milk is possetted harmlessly upon the sheet

Premature babies regurgitate more easily than full-term infants, and some experienced nurses have learned to overcome this tendency by nursing them in the prone position. And the radiologist can demonstrate that the one position in which the infant cannot regurgitate an opaque meal is semi-prone on his right side.

Incidentally, this is a much more effective way of posturing the infant with cardiochalasia or hiatus hernia, particularly if the infant is tilted by raising the head of the cot on 18-inch blocks

London N.W.3
R J K BROWN

SIR,—Using the guineapig, an animal well known to be peculiarly immunologically fragile, Dr Camps and his colleagues (Nov 19) have nevertheless demonstrated as close an analogous pathogenetic explanation of the " cot-death syndrome " in infants as we are ever likely to get The fact that most infants fed on cow's milk develop antibodies to the proteins of that milk is proffered as another inducement to breast-feed young babies wherever practicable

Is it then true, as would seem to be implied, that infants fed their mother's milk do not develop antibodies to human milk proteins ?

Group Pathological Laboratory,
Royal Hampshire County Hospital,
Winchester

T J Muckle

POSSIBLE SITE OF BIOCHEMICAL ERROR IN GAUCHER'S DISEASE

Sir,—Gaucher's disease, a familial disorder of lipid metabolism, results in the accumulation of a cerebroside in the cells of the reticuloendothelial system This cerebroside is composed of a long-chain fatty-acid attached to sphingosine with an acid amide link Galactose is attached to the end of the sphingosine with a glycoside link The cerebroside is called kerasin if its fatty-acid is lignoceric acid, although other fatty-acids can be present In some cases of Gaucher's disease, an abnormal kerasin has been found with glucose in place of the usual galactose portion of the molecule In other cases the normal galactose cerebroside accumulates

On the assumption that an enzymatic defect in cerebroside metabolism is responsible for the accumulation of cerebroside in Gaucher's disease, we have studied the incorporation of ^{14}C-labelled glucose and galactose into the microsome-supernatant fraction of a normal spleen and a spleen from a patient with Gaucher's disease according to the method of Burton et al [1]

Spleens obtained at *splenectomy of a boy with Gaucher's disease and from a normal boy with a ruptured spleen due to a sled accident* were immediately frozen with dry ice-ethanol and stored at −10°C in a deep-freeze until used After homogenation of 4 8 g of spleen with 20 ml of 0 25 *M* sucrose, the microsome-supernatant fraction was separated by centrifugation in a Lourdes centrifuge at 0°C A portion of the microsome-supernatant fraction was rapidly heated and maintained at 50°C for 2 minutes and then placed in an ice bath with the unheated portion until used To each 0 9 ml aliquot of the microsome-supernatant fraction was added 0 1 ml $MgCl_2$ solution ($5 5 \times 10^{-3}$ *M*), 0 1 ml adenosine triphosphate (A T P) solution ($5 5 \times 10^{-3}$ *M*), 0 1 ml uridine triphosphate (U T P) solution *($5 5 \times 10^{-3}$ M)* and either 0 1 ml glucose-U-^{14}C (glucose uniformly labelled with ^{14}C) solution ($8 3 \times 10^{-4}$ *M*, 0 33 mC per mmole) or 0 1 ml galactose-1-^{14}C ($1 1 \times 10^{-3}$ *M*, 0 25 mC per mmole)

After *incubation at 37°C under a mixture* of 95% N_2 and 5% CO_2 for two hours, 20 ml of chloroform-methanol (2 1) was added to each vessel and brought to a boil to stop enzymatic activity To each vessel was added 0 1 *g* of crude cerebroside to facilitate extraction The cerebrosides were isolated by passing the solution over a mixed-bed column of Dowex 1 and Dowex 50, layered with Florisil modified after Radin et al [2] Each eluate was taken to dryness, dissolved in 10 ml chloroform methanol (2 1) and washed 5 times with 10 ml of chloroform-saturated methanol water *(1 1) Each precipitate* was dissolved in chloroform-methanol (2 1) and evaporated in a warm water-bath to 1 5 ml , plated, and the radioactivity counted

The mean incorporation of sugar in *microsome-supernatant* fraction (counts per min per 100 mg cerebroside ± S E) was

	Glucose U ^{14}C	*Galactose 1-^{14}C*
Normal spleen	34 6±5 5	36 7±16·9
Gaucher spleen (unheated)	100·9* ±6 2	106 1* ±5 3
Gaucher spleen (heated)	93 6† ±3 7	213 7 ±14 4

* *Differ significantly ($P<0·01$) from normal spleen*

† Differs significantly ($P<0 01$) from galactose incorporation (heated)

‡ Differs significantly ($P<0 01$) from galactose incorporation (unheated)

Both glucose and galactose were incorporated to a significantly greater extent in the Gaucher spleen cerebroside than in the normal Heating resulted in no significant difference in the incorporation of *glucose into* Gaucher spleen cerebroside, but did result in a significantly greater incorporation of galactose.

From these results, we propose that the first step is the addition of glucose rather than galactose to the acceptor substance *It* has been shown by others that the acceptor substance is sphingosine and that the fatty-acid is added after addition of the hexose In turn, the glucose cerebroside is converted to galactose cerebroside through catalysis by a heat-sensitive epimerase enzyme. A *defect* in this epimerase enzyme in Gaucher's disease would result in the accumulation of the glucose cerebroside. An enzymatic defect in the catabolism of galactose cerebroside would explain those cases in which galactose cerebroside is found to accumulate

This study was aided by U S P H S grants A-2504 (c1) and 2G-346 (s1)

Department of Pediatrics,
State University of New York,
Upstate Medical Center,
Syracuse

Marvin H Stein
Lytt I Gardner

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1 Burton R M , Sodd M A Brady R O *J biol Chem* 1958, 233 1053
2 Radin N S , Lavin F B , Brown J R *ibid* 1955 217 789

β-GLUCURONIDASE ACTIVITY OF CORONARY ATHEROSCLEROTIC PLAQUES

Sir,—In view of the present controversy about the pathogenesis of atherosclerotic lesions, increasing attention is now being given to the arterial intima and the intimal reactions in various types of atherosclerotic plaques Our studies have included the examination of arterial lesions by the surface preparation technique,[1] tissue culture of arterial intima, and enzymological analyses of atherosclerotic plaques It is the results of this third method which we report here

In an analysis of coronary atherosclerosis with special reference to occlusive thrombi [2] it was also found that the fully developed atherosclerotic lesions could be divided into two distinct histological types

(1) The crescent-shaped hard lesion composed of *laminated* layers of collagen and fibrin

(2) An essentially fatty lesion composed almost entirely of sudanophilic material, separated from the circulating blood by a thin film of endothelium or fibrin

Furthermore, transverse sections of coronary arteries from a large number of cases have shown that the earliest lesion in the development of *atherosclerosis is the accumulation of acid* mucopolysaccharide in the intima Consequently in this enzymological investigation the plaques were classified in three groups

(1) The active proliferative lesion—*rich in acid mucopolysaccharide* and showing various degrees of fibroblastic proliferation

(2) The hard fibrocollagenous lesion

(3) The fatty or soft plaque

It was decided to estimate the *β-glucuronidase* activity in these three types of lesion because it has been suggested that β-glucuronidase plays an active role in cellular proliferation and tissue regeneration,[3] and as β-glucuronidase catalyses the hydrolysis of glucuronides it may play a part in the metabolism of glucuronic acid, a molecular constituent of the acid mucopolysaccharide of arterial intima

The β-glucuronidase activity was therefore estimated in normal intima and in intima in the three main types of atherosclerotic lesion described above in 160 men and 160 women The method was *a modification of that given by* Talalay et al [4] and results are expressed as μg of activity per g of tissue per hour

Type of arterial lesion (40 in each group)	*Mean β-glucuronidase activity (μg per g per hr)*	
	Men	*Women*
Normal intima	30	50
Active proliferative lesion	700	840
Hard collagenous lesion	390	520
Soft or *fatty* lesion	200	290

These findings indicate

(1) The active proliferative lesion, rich in ground substance and showing active fibroplasia, has the highest enzymic activity

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1 Lautsch, E V McMillan, G G , Duff, G L *Lab Invest* 1953 2, 397
2. Branwood A W Montgomery G L *Scot med J* 1956 1, 367
3 Levvy, G A Kerr L M H Campbell, J G *Biochem J* 1948 42, 462
4 Talalay, P , Fishman W H , Huggins C *J biol Chem* 1946 166 757

(2) This activity decreases as the plaques become more collagenous and less cellular

(3) The accumulation of lipid to form the fatty plaques is associated with a marked reduction in enzyme activity

(4) The mean enzymic activity of normal intima and of all plaques is higher in women than in men

These results are largely confirmed by Dyrbye and Kirk,[5] who showed that the β-glucuronidase activity of normal coronary-artery intima had a mean value of 55 units They did not comment, however, on any sex variation in the enzymic activity in their series of normal coronary-artery intima

Department of Pathology,
University of Aberdeen,
Foresterhill, Aberdeen

A W Branwood
A J Carr

Parliament

Medical Termination of Pregnancy Bill

Mr Kenneth Robinson has introduced a Bill to amend the law relating to the termination of pregnancy by registered medical practitioners It will be read a second time on Feb 10

QUESTION TIME

Hospital Staff Shortage

Lord Stonham asked H M Government whether they were aware that in the North East Metropolitan regional hospitals the total staffs of physiotherapists are 32 7%, and psychiatric social workers 31 4% below establishment, that there was an almost equally acute shortage of radiographers, pharmacists, and almoners, that the position had greatly worsened since the beginning of the year, and what steps they would take to effect an improvement —Lord Newton replied The Government are aware that many hospital authorities find difficulty in filling their establishments for these classes of staff and that these difficulties are greater in some areas than in others These professions are in competition with a number of other important professions, both inside and outside the National Health Service, and there are not enough young people of suitable calibre to fill all the available posts For those whose training takes place in the National Health Service hospitals, recent figures of student recruitment are encouraging, and where specific difficulties, such as inadequate training facilities, hamper recruitment, the Government are prepared to consider how they can help Salaries are a matter, in the first instance, for the appropriate National Health Service Whitley Council, but the salaries of all the classes mentioned have been substantially increased in the past two years

Lord Stonham Is the noble Lord aware that despite the increased salaries which have been paid, the conditions are now disastrous, that the number of vacancies has increased since the beginning of last year by 50% in many cases and in some it has doubled, and that unless something very radical is done to bring about an improvement the hospital service is going to be seriously impaired?—Lord Newton The noble Lord has great experience of these problems and he knows that it is the responsibility of hospital management committees to recruit their staff But the Government are only too anxious to help in any way they can to solve these difficulties, and would welcome any suggestions As I said in my earlier answer, the recruiting figures are now encouraging I believe the reason for that is we are now beginning to see the results of the rise in the birth-rate which began in 1941 But it is true, of course, that the demand for these professions is expanding all the time as hospital facilities expand, and there is competition all the time for suitable people to fill these places

Lord Amulree Although admittedly there has been some increase in salaries, does not the noble Lord think the salaries should possibly be made more commensurate with what these young girls can get in commerce?—The Earl of Lucan The noble Lord in his first answer mentioned training within the National Health Service and said the figures were now encouraging, but would he not agree that many of those who get their training in the health service afterwards leave for better-paid employment in industry?—Lord Newton It is true that there is a good deal of wastage (to use a technical term), but I believe that this is largely because of marriage, and most of the members of these professions are, of course, women All these five groups have received substantial salary increases within the past two years, and for none of them, at the moment, is a claim for a general pay increase before the appropriate Whitley Council The trouble is that if, in due course, their salaries were increased substantially, those salaries would be met and matched by rises in the salaries of some of the other professions which compete for these people Lord Stonham I am grateful to the noble Lord for his second answer to me and for the way he tried to meet the position, but I can assure him that the trouble is not marriage, it is salaries I feel that the main obstacle is the fact that the Whitley Council machinery has virtually seized up

Lord McCorquodale of Newton I wonder whether I might suggest that part of the difficulty is the extension of the amount of knowledge that some of these people have to acquire before they get the appropriate degree or qualification, some of which knowledge is of not the slightest use to them afterwards I am sure that less skilled procedure might lead us to more practical expertise in this matter

Hospital Voluntary Funds

Dr Donald Johnson asked the Minister of Health what steps he was taking to encourage voluntary help in the raising of funds towards the financing of projects for new hospitals or new hospital departments —Mr Enoch Powell replied It is my hope that all concerned with the development of the hospital service will not fail to make full use of contributions towards it which voluntary funds may offer Dr Johnson Is the Minister aware of the general impression that voluntary funds for hospitals can be used only for purposes not directly connected with the running of the hospitals, such as patients' comforts? Will he take all possible steps to dispel this impression? Mr Powell I hope that the question and my reply will help to do that Dr Edith Summerskill In view of the fact that successful voluntary effort depends on local circumstances, does not the Minister think that there should be some central supervision in order that all hospitals may be treated equitably? Mr Powell What I have said is not inconsistent with the necessity for central supervision

Representation of Consultants

Mr L A Pavitt asked the Minister if he would give recognition to the council of the Regional Hospitals' Consultants and Specialists Association as being representative of the majority of consultants and specialists in the National Health Service, and if he would consult with the medical profession in order to secure a review of the constitution of the staff side of the Whitley Committee B to give a fairer balance between teaching and regional hospital representatives Mr Powell No, Sir As regards the second part of the question, this is a matter for the staff side concerned Mr Pavitt Is the Minister aware that 85% of the consultant specialists are working with regional hospitals, and not in teaching hospitals, and that 90% of the clinical work is being done by these consultant specialists in the regions? Why should not they have their proper place on all committees, including the Whitley Committee? Mr Powell I am aware of the facts which the hon Member mentions, but I am satisfied that the Joint Consultants' Committee adequately represents these consultants

Treatment of Foreign Visitors

Mr Albert Evans asked the Minister if he would state the number of cases brought to his notice of foreigners entering, or attempting to enter, this country for the purpose of medical treatment under the National Health Service Mr POWELL In 1959, 1503 aliens were reported as entering, or attempting to enter, this country for medical treatment 6 of these were refused entry Steps were taken to ensure that the remainder paid for the treatment Mr EVANS Will the Minister assure the House that in this matter he will follow the policy of all those Ministers who have held office since the inception of the National Health Service scheme? Will he refrain from looking at this matter from a narrow nationalistic point of view or with the idea of making petty economies? Mr POWELL This thing is an abuse However relatively small the cost, it ought, so far as is practicable, to be prevented There has been no difference in policy in this matter since the original Act

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[5] Dyrbye, M , Kirk, J E *J Gerontol* 1956, **11**, 33

Mr MICHAEL FOOT Is the Minister aware that when the service was first introduced the idea of giving treatment to sick foreigners was not regarded as an abuse but that we gloried in it? Mr POWELL There has never been any question of persons from abroad who fall sick in this country receiving attention under the National Health Service That has not been in question from either side of the House But it is not in accordance with the intention of the Act that aliens should come to this country for the purpose of getting treatment under the Act

Remploy and the Mentally Disordered

Lord STONHAM asked H M Government if, in areas where suitable facilities were available, it would be possible for Remploy to act as agents for local health authorities in discharge of their responsibilities under the Mental Health Act, to provide training and occupation for the mentally disordered —The Earl of DUNDEE, the Minister Without Portfolio, replied My Lords, Remploy already provide employment for a number of mentally disordered persons The company will continue to consider persons handicapped by mental disorders, together with other disabled persons for vacancies in Remploy factories, but it has no power to act as agents for local health authorities in the provision of training or occupation Lord STONHAM Is the noble Earl aware that my question invites consideration of granting such powers to Remploy? I would ask him to look at this matter again, particularly—having regard to the tremendous success of Remploy—with a view to seeing whether the Remploy sales organisation could not be used to dispose of the products of these centres, and in that way give the mentally disordered people a chance of earning at least part of their living instead of being in merely therapeutic centres The Earl of DUNDEE I am very grateful to the noble Lord for his appreciation of the excellent work which is being done by Remploy They do employ, out of a total of 6300, I think about 500 people who are suffering from various kinds of mental or nervous disorders, and in view of the possibility of some of the persons placed by local authorities in special centres being able to go to Remploy afterwards very close touch is maintained But that is not quite the same as giving the primary responsibility to Remploy for the care of mentally disordered people Lord STONHAM Is the noble Earl aware that what I have in mind is that in these local authority centres mentally disordered people will make something and it is absolutely essential that it should be sold by a skilled organisation, otherwise they will be at the mercy of charitable disposals and it will not be a really serious project Would he consider that possibility? The Earl of DUNDEE I gather the noble Lord is thinking of more efficient arrangements for the sale of their products, and I will most certainly look into that

Poliomyelitis Vaccination

Poliomyelitis vaccine is now sufficiently plentiful to permit vaccination of those aged 40 and over who are not covered by the existing arrangements From Jan 1, family doctors will be able to vaccinate any such person who, they consider, requires this protection

Children Remanded to Prison

During the nine months ended Sept 30, 1960, in England and Wales, 585 boys and 23 girls under seventeen years were remanded to prison instead of being sent to remand homes

Obituary

WALTER WEIR GALBRAITH

M B Glasg, F R F P S, F R C S E

Mr Walter Galbraith, consulting surgeon to the Western Infirmary, Glasgow, and a former president of the Royal Faculty of Physicians and Surgeons of Glasgow, died on Nov 25 at the age of 71

Born in Glasgow, he was the eldest son of the late W B Galbraith, J P, C A, and a brother of Lord Strathclyde He was educated at Glasgow Academy and the Leys School, Cambridge In 1914 he graduated M B from the University of Glasgow, and during the 1914-18 war he served overseas as a surgical specialist

On demobilisation he was appointed to the staff of the Western Infirmary in Glasgow and rapidly earned a reputation as a gifted and courageous general surgeon He early found his special interest in urology, and he was largely responsible for setting up a department of urology in the Western Infirmary

He was also active in the affairs of his profession, his specialty, and his medical school In 1949 he was president of the British Association of Urological Surgeons, and the following year he became president of the Royal Faculty of Physicians and Surgeons of Glasgow At the time of his death he was a vice-president of the Royal College of Surgeons of Edinburgh He was a member of the Scottish Health Services Council and for many years represented the Royal Faculty on the Joint Consultants' Committee and on the medical Whitley Council

When he retired from practice in 1954 he made his home near Troon There he found much pleasure in gardening and in the sports in which he excelled—golf, fishing, and shooting Yet he accepted his leisure as an opportunity for further service He continued as a member of the Joint Consultants' Committee, as a governor of Glasgow Academy, and as a director of the McAlpin Nursing Home, and he accepted two new charges in membership of the Western Regional Hospital Board and of the court of Glasgow University

A B K writes

"Under Walter Galbraith's leadership the department of urology at the Western Infirmary made many contributions to the advance of surgery Yet he will be remembered perhaps more for his generous personality which did so much to foster a happy relationship among the urological departments in the city No visitor to his department was allowed to leave without being pressed to see the work of the others He travelled extensively at home and abroad with urologists and with general surgeons He revelled in companionship His friendly interest strengthened many a younger man His blunt but kindly criticism stimulated many a contemporary His opinions were often based on emotion rather than on regulations They were valued for their sincerity and humanity To everything which he did he brought an unsurpassed gift for fellowship He will be mourned by an innumerable company of friends"

S A pays tribute to him as a Scot as well as a surgeon

"Walter's shrill and arresting 'What?' was like a pistol shot It was the opening snap of cerebration By the time the startled and discomfited colleague had filled diastole with a twice-told tale, Walter had formed an opinion—and a shrewd one at that This idiosyncrasy epitomised much of his character Essentially he was a man of business, a man of affairs, but schooled in the discipline of surgery, and in his chosen craft he was a master His outward cheerfulness and boisterou bonhomie were perhaps acquired in the interests of his friends Behind this carefree style there was the astute brain of the relentless Scot—vigorous by disposition, yet able to carry the chains of convention and caution with relish rather than with dismay The technical precision of the surgical specialist was complementary to the assiduousness of the committee-man Purposive, tireless, and intensely patriotic, Scotland was his eyrie—and there he brooded like a golden eagle, jealously maintaining and defending the prestige of medicine in a changing world."

Mr Galbraith is survived by his wife, a son, and two daughters

Public Health

Foot-and-mouth Disease

THE present outbreak of foot-and-mouth disease [1] continues to spread despite all precautions At midnight on Friday, Nov 25, the Ministry of Agriculture announced that the movement of farm animals and the holding of markets was restricted in all counties of England north of a line from Bristol to London, with the exception of Cumberland and Westmorland. This widespread restriction was imposed because, during Friday, foot-and-mouth had been confirmed in Nottinghamshire, Essex, and Shropshire, and the outbreaks there could not be connected with any of the earlier cases

By Monday, Nov 28, a 9th case of foot-and-mouth disease had been confirmed in the Orkneys, bringing the number of outbreaks in Scotland to 66 The United Kingdom total was then 193 3 more cases were confirmed during the day

So far, the disease has not spread to Eire, but the Department of Agriculture in Dublin has asked farmers, cattle-buyers, and others who have any contact with livestock or meat in Britain not to visit Ireland until the present crisis is over

There will be no livestock at this year's Smithfield Show, for the first time since 1798

Up to Nov 28, 14,700 cattle, 16,750 sheep, 6700 pigs, and 25 goats had been slaughtered

Industrial Biological Research Association

A new research organisation—the British Industrial Biological Research Association—has been formed to study the possible effects on health, and to ensure the harmlessness, of substances which may be ingested in food, drink, and cosmetics Supported by several leading companies, it is welcomed by interested Government departments and will receive a grant from the Department of Scientific and Industrial Research

The Association s main object is the establishment of a biological research station for investigating the effect of substances used in food manufacture, either as processing aids for or flavouring and colouring food, as well as those which may get into food from pesticides, from plant used in food manufacture, from packaging materials, or from utensils The Association hopes to build its laboratories at Leatherhead, Surrey, on land leased from the British Food Manufacturing Industries Research Association, which has offered to share some facilities and administrative services in the initial stages The temporary headquarters of the Association are at 11, Green Street, London, W 1

Classification of Occupations

Classification of Occupations [2] has been compiled by the General Register Office, England and Wales, and the General Registry Office, Scotland, primarily for use in the Census on April 23, 1961 It is also being used by the Registrars General for coding occupations stated at the registration of deaths and in morbidity surveys and inquiries The *Classification* is published in the hope that it will be of interest to research-workers who may wish to relate their results to the Census statistics

Diary of the Week

DEC 4 TO 10

Sunday, 4th

Institute of Laryngology and Otology, 330 Gray's Inn Road, W C.1
10 15 A.M. Mr Wallace Black Common Ear, Nose, and Throat Conditions

Monday, 5th

University College London, Gower Street, W C.1
5.30 P M Prof W S Feldberg Mediators of Allergic Reactions

Postgraduate Medical School of London, Ducane Road, W 12
4 P M Dr J F Goodwin Effect of Drugs on the Pulmonary Circulation.

Tuesday, 6th

Royal Society of Medicine, 1, Wimpole Street W 1
5 30 P M *Pathology* Prof N F Maclagan Changing Views on Jaundice. (Presidential address)
8 30 P M. *Orthopædics* Mr Walpole Lewin Mr R. C Connolly, Prof Roland Barnes, Mr F C Durbin Injuries of the Head and Neck.

British Postgraduate Medical Federation
5 30 P M (London School of Hygiene and Tropical Medicine Keppel Street W C 1) Prof D G Catcheside Functional Structure of Genes

Institute of Obstetrics and Gynaecology
3 P.M. (Hammersmith Hospital Ducane Road, W 12) Mr J A Stallworthy Carcinoma of the Uterus

St Mary s Hospital Medical School, W 2
5 P.M (Wright-Fleming Institute.) Mr Aleck Bourne Some of My Mistakes

West End Hospital for Neurology and Neurosurgery, 91, Dean Street, W 1
5 30 P M Mr K. I Nissen Orthopædic Surgery of Spastic States

Royal Army Medical College Millbank S W 1
5 P M Prof F A. R. Stammers Pain in the Arm

Research Defence Society
5 30 P M. (University College London, Gower Street, W C 1) Prof J H. Burn Testing Drugs on Man. (Stephen Paget lecture)

Leeds Neurological Sciences Colloquium
5 15 P M (General Infirmary at Leeds) Dr Eliot Slater Schizophrenic-like Psychoses of Epilepsy

Wednesday, 7th

Royal College of Surgeons of England Lincoln s Inn Fields, W C 2
2 30 P M Sir Stanford Cade Malignant Melanoma. (Bradshaw lecture.)

Royal Society of Medicine
5 15 P M *History of Medicine* Mr Dickson Wright History of Opium
8 P M *Surgery* Mr G A Mason Mr Charles Drew, Mr A J Cokkinis Mr G E Mavor Coronary and Mesenteric Vascular Occlusion.

Postgraduate Medical School of London
2 P.M Dr A. E Kellie Steroid Assays

Institute of Dermatology Lisle Street, W C.2
5 30 P.M. Dr R. W Riddell Yeasts as Pathogens

Institute of Diseases of the Chest Brompton, S W 3
5 P.M Mr Matthias Paneth Surgery of Secundum Defects of the Atrial Septum

Institute of Obstetrics and Gynaecology
2 P M (Queen Charlotte s Hospital, Goldhawk Road W 6) Mr G B Gibson Postmaturity

Royal Institute of Public Health and Hygiene, 28 Portland Place, W 1
3.30 P.M Dr Kenneth Soddy World Mental Health Year—International Trends in Mental Health Work.

Midland Medical Society
8 30 P M. (Birmingham Medical Institute 36, Harborne Road Birmingham, 15) Dr R. Bodley Scott Acute Leukæmia—the Present Therapeutic Position.

Thursday, 8th

Royal College of Physicians of London Pall Mall East S W 1
3 P.M. Sir George Clark Thomas Linacre. (Commemoration of the Quincentenary of Linacre s birth.)

Royal College of Surgeons of England
5 P.M Mr H J Seddon Manchester Ship Canal and Colonial Frontier (Robert Jones lecture.)

University College London
5.30 P.M. Sir Solly Zuckerman Social Function of Science—1960 (Rickman Godlee lecture)

British Postgraduate Medical Federation
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr E. J L Lowbury Drug Resistance and the Response to Chemotherapy

Institute of Dermatology
5 30 P.M. Dr P F Borrie Disorders of Function in Cutaneous Blood Vessels and Lymphatics

Institute of Obstetrics and Gynæcology
4.30 P.M (Chelsea Hospital for Women Dovehouse Street, S W.3) Miss J A. M Moore Dysmenorrhœa.

Royal Society of Tropical Medicine and Hygiene, 26 Portland Place, W 1
7.30 P.M. Dr S Stott Dr E van Oye Dr Henry Foy Hookworm Diseases

Alfred Adler Medical Society
8 P.M. (11 Chandos Street W 1) Dr Wilfred Barlow Anxiety and Muscle Tension.

Honyman Gillespie Lecture
5 P.M (University New Buildings Teviot Place Edinburgh) Prof M. L. Rosenheim Small Kidney

Friday, 9th

Postgraduate Medical School of London
10 A.M. Dr Victor Wynn Metabolic Care of the Surgical Patient.
4 P.M. Dr John Badenoch Malabsorption Syndromes

Institute of Laryngology and Otology
3.30 P.M. Dr Norman Hulbert Headache and Facial Pain

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[1] See *Lancet* Nov 26 1960 p 1183

[2] Classification of Occupations 1960 H M Stationery Office Pp 136 27s 6d

Notes and News

DOCTORS AND NATIONAL SERVICE

THE Minister of Labour stated in the House of Commons on Nov 18 that men who had received enlistment notices instructing them to report to their units the previous day were the last to be called up and no further enlistment notices would be issued

The Central Medical Recruitment Committees have already been able to meet the requirements of H M Forces for medical officers up to the end of this year No further nominations to the Forces will be made, and any doctor who has not already been notified of his nomination to the Forces will not now be required for National Service

Any doctor who wishes to consider a Regular commission in the Armed Forces should apply directly to the Service of his choice [Medical Director-General of the Navy (Admiralty), Queen Anne's Mansions, London, S W 1, the Under Secretary of State, War Office (A M D 2), Lansdowne House, Berkeley Square, W 1, the Under Secretary of State, Air Ministry (M A 1), 1, Tavistock Square, W C 1]

The principal task of the Central Medical Recruitment Committees has thus come to an end During the period 1939–60, the committees recruited more than 27,000 doctors for service in H M Forces

VISITORS FROM CHINA

REPRESENTING the Chinese Medical Association, six Chinese doctors are now visiting this country on the invitation of the Royal College of Physicians of London The head of the delegation, Dr Hsueh Kung-Chuo, is vice-president of the Chinese Academy of Medical Sciences, and the members are Prof Chang Si-Chun and Prof Liang Chih-Chuan of the Academy, Prof Chu Ti-Tung and Dr Lan Si-Chun of Shanghai, and Dr Chu Shou-Ho of Peking They are likely to be in Britain until Dec 14

HANDICAPPED CHILDREN

Princess Margaret, presiding at the 72nd annual general meeting of the Invalid Children's Aid Association, at St James's Palace on Nov 22, referred to a plan for a new school for "non-communicating" children, unable to speak because of profound emotional disturbance and specially studied by Dr Louis Minski at Belmont Hospital She said that about 9000 handicapped children had been helped last year, with 15,000 visits and interviews

The annual report deals mainly with the Association's schools, and in moving its adoption Dr A White Franklin, the chairman, spoke of the need for money to finance new schoolrooms at the Meath Home, Ottershaw, at Pilgrims School, Seaford, and at Brentwood, St Leonards Pioneer work is being done at the John Horniman School, Worthing, for children needing residential intensive speech training from the age of 5 "Case work remains an important activity The time has come for a combined case-work unit where the family could come in trouble and be helped as a family A review of results should show whether case work is more effectively carried out by a general worker or by a specialist worker with a vocation such as for children, old people, or marital problems Whatever the conclusion, workers and their parent associations would benefit from sharing work in a common centre"

The Earl of Feversham gave an address on Mental Health, describing the demands of life today, the scale and the cost of breakdown, and the mental makeup and basic needs of the individual There are 200,000 people in mental and mental-deficiency hospitals (about half the hospital population), and one child in every twenty will need "mental treatment" some time in life The only course at present is to help the individual to adjust to the environment, although research into physical and chemical influences on the brain is being carried out In the presence of physical handicap, adjustment must include parents as well as child The foundations of good family life are discipline, security, constancy, and a moral tradition arising from religion and background

APPROVED NAMES FOR DRUGS

THE British Pharmacopœia Commission has issued the following new supplementary list of approved names

Approved name	*Other names*
Amphomycin	An antibiotic produced by *Streptomyces canus*
Betamethasone	9α Fluoro-11β 17α 21 trihydroxy 16β methylpregna 1 4-diene 3 20-dione 9α-Fluoro-16β methylprednisolone
Biperiden	1 (*bicyclo*[2 2 1]Hept 5 en 2 yl) 1 phenyl 3 piperidinopropan-1 ol The name Akineton is applied to the hydrochloride and the lactate
Chlordantoin	5-(1-Ethylpentyl) 3 (trichloromethylthio)-hydantoin
Chlordiazepoxide	7 Chloro-2 methylamino 5-phenyl 3H benzo 1 4-diazapine 4-oxide Librium is the hydrochloride
Chlorprothixene	α 2 Chloro 9 (3 dimethylaminopropylidene)-thiaxanthen Taractan
Chlorthalidone	3-(4 Chloro-3 sulphamoylphenyl)-3 hydroxy-*iso*indolin-1 one Hygroton
•Clonitazene	2 *p* Chlorobenzyl 1 (2 diethylaminoethyl) 5-nitrobenzimidazole
Demecarium Bromide	Decamethylenebis(*m* dimethylaminophenyl *N* methylcarbamate) dimethobromide Humorsol
Dioxamate	4-Carbamoyloxymethyl 2 methyl 2 nonyl 1 3-dioxolan
Ectylurea	α-Ethylcrotonylurea Nostyn
Ethchlorvynol	5 Chloro-3-ethylpent 1 en-4 yn 3-ol Placidyl
Ethosuximide	α Ethyl-α methylsuccinimide Zarontin
•Etonitazene	2 *p*-Ethoxybenzyl 1 (2 diethylaminoethyl)-5-nitrobenzimidazole
Hexapropymate	1-Propynyl*cyclo*hexyl carbamate Merinax
Hydromorphinol	14 Hydroxydihydromorphine
Isoaminile	4 Dimethylamino-2 *iso*propyl 2 phenyl valeronitrile Dimyril is the citrate
Isoxsuprine	1-*p*-Hydroxyphenyl 2 (1 methyl 2-phenoxyethyl amino)-1-propanol Dilavase is the hydrochloride
Methicillin	6-(2 6 Dimethoxybenzamido)penicillanic acid Celbenin is the sodium salt Staphcillin is the sodium salt
Oxymetholone	2 Hydroxymethylene 17α methyldihydro-testosterone Anapolon
Pemoline	2 Imino-5 phenyloxazolidin-4-one Kethamed Pioxol
D Penicillamine	(−)-ββ Dimethylcysteine
Phenbutrazate	2 (3-Methyl 2 phenylmorpholino)ethyl α phenylbutyrate
Phendimetrazine	(+) 3 4 Dimethyl 2 phenylmorpholine Plegine is the tartrate
•Phenoperidine	Ethyl 1 (3 hydroxy 3 phenylpropyl)-4-phenylpiperidine 4 carboxylate
Pipazethate	2 (2 Piperidinoethoxy)ethyl 10-thia 1 9-diaza anthracene 9 carboxylate Selvigon is the hydrochloride
Plasminogen	The specific substance derived from human plasma which when activated, has the property of lysing fibrin
Pyrazinamide	Pyrazinoic acid amide
Sodium Ironedetate	Iron chelate of the monosodium salt of ethylenediamine N N N N tetra acetic acid Sytron
Streptodornase	An enzyme obtained from cultures of various strains of *Streptococcus haemolyticus* and capable of catalysing the depolymerisation of polymerised deoxyribonucleoproteins
Streptokinase	A co-enzyme obtained from cultures of various strains of *Streptococcus haemolyticus* and capable of changing plasminogen into plasmin
Tranylcypromine	(+) *trans* 2 Phenylcyclopropylamine Parnate is the sulphate

• Narcotic substances which fall under international control and are no available as therapeutic agents

INDEX

Proprietary name	*Approved name*	*Proprietary name*	*Approved name*
Akineton	Biperiden	Nostyn	Ectylurea
Anapolon	Oxymetholone	Parnate	Tranylcypromine
Celbenin	Methicillin	Pioxol	Pemoline
Dilavase	Isoxsuprine	Placidyl	Ethchlorvynol
Dimyril	Isoaminile	Plegine	Phendimetrazine
Humorsol	Demecarium Bromide	Selvigon	Pipazethate
Hygroton	Chlorthalidone	Staphcillin	Methicillin
Kethamed	Pemoline	Sytron	Sodium Ironedetate
Librium	Chlordiazepoxide	Taractan	Chlorprothixene
Merinax	Hexapropymate	Zarontin	Ethosuximide

CLINICAL RESEARCH LABORATORIES AT BIRMINGHAM

On Nov 15 Sir Henry Dale, chairman of the Wellcome Trust, opened the Wellcome Wing of Clinical Research at the Queen Elizabeth Hospital, Birmingham. The four-storeyed wing, which houses the laboratories for the whole-time clinical departments of the University of Birmingham, has cost £117,000 The Trust gave £95,000 for the building, and the University Grants Committee has provided the scientific equipment.

Surgery is housed in the top two storeys The lower of these has a laboratory, 34 ft by 50 ft with bench-space and two screened-off portions with fume-cupboards, a small laboratory fitted for intestinal work, an office cum laboratory, and a seminar room to seat 50 people, fitted with projector services and a small library On the top floor is an operating-theatre that will take all the monitoring apparatus necessary for experimental open-heart work, and can also accommodate four tables for simpler work The sound-proof, plenum-ventilated and heated kennel-room will take 18 dogs, and there is a kitchen opposite for the preparation of their food There are also two laboratories for isotope work, one with a fume-chamber, and a large electronics laboratory where at the moment work is being done on apparatus for open-heart surgery and cardiac arrest, and on inducted pace makers for the treatment of Stokes-Adams disease, &c. There is also a technician s room.

Current research on the surgical side includes the biochemistry of wound healing, hypersensitivity and auto-immunity as factors in non-specific intestinal granulomata, the reaction of the suprarenal cortex to surgical stress, portal and systemic venous levels of 5 hydroxytryptamine in intestinal disease, exfoliative cytology in upper and lower bowel disease, and the pattern of collateral circulation after coronary disease and surgical devices for improving this

On the medical floors research is being carried on into such aspects of the cardiopulmonary system as normal and abnormal alveolar capillary gradients in the lungs, the early functional changes in chronic bronchitis, metabolic exchanges between the peripheral muscles and the myocardium under varying conditions, and intestinal absorption with particular reference to the use of the stable isotope nitrogen 15

PREVALENCE OF RHEUMATIC DISORDERS

In this country the prevalence of rheumatoid arthritis at any one time is 2 5% in men and 6 1% in women This estimate was given by Dr J S Lawrence, director of the Empire Rheumatism Council's field survey unit, at a press conference in London on Nov 24 The estimate is based on a detailed four-year survey of 1700 people in an urban area and of 900 in a rural area. This survey also showed that at 65 some 97% of men and 98% of women have X-ray evidence of osteoarthritis, though in about 35% of these cases the disease causes no incapacity The prevalence of spondylitis in the population as a whole is estimated at 0 3%, and the prevalence of gout is likewise put at 0 3% The survey brought to light two significant findings first, that there is a hereditary tendency in some forms of rheumatoid arthritis, and secondly that 1 person in about 20 suffers at some time from acute rheumatism or polyarthritis, resembling rheumatic fever but not affecting the heart [1]

Dr W S C. Copeman, chairman of the Council, commenting on the survey, remarked that it indicated that in Britain at any one time 5,726,000 people—that is, just over 14% of the adult population—have one of these severe forms of arthritis Obviously, he said, we need more and better hospital facilities for treatment, more doctors trained to cope with these diseases, and more research

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H. J McCurrich Prize

The Regional Hospitals' Consultants and Specialists Association is offering this prize (100 guineas) in 1962 for an essay on a medical or surgical topic written by " qualified hospital staff up to and including senior registrars " during tenure of office in hospitals in England and Wales Further details may be had from the secretary of the Association, 47, Lincoln's Inn Fields, London, W C 2

University of London

Dr Denis Hill, senior lecturer in the department of clinical neurophysiology at the Institute of Psychiatry and lecturer in psychological medicine at King's College Hospital Medical School, has been appointed to the chair of psychiatry at Middlesex Hospital Medical School

Dr Hill, who is 47 years of age, was educated at Shrewsbury School and St Thomas's Hospital. After qualifying in 1936 he held a house-appointment at Bethlem Royal Hospital and in 1938 he became chief assistant in the department of psychological medicine at St. Thomas s During the late war he was a psychiatric specialist in the Emergency Medical Service In 1947 he was appointed physician and lecturer in psychological medicine at King's College Hospital and in 1948 he was appointed to the staff of the Institute of Psychiatry and the Maudsley Hospital He was elected F.R C.P the following year From 1956 to 1960 he was a member of the Medical Research Council In 1950 he edited a symposium on Electroencephalography and he has also published papers on its applications to psychiatric problems, on medical education, and on the place of psychiatry in medicine

Mr Ian MacGillivray, senior lecturer in the department of midwifery in the University of Aberdeen, has been appointed to the chair of obstetrics and gynæcology at St Mary's Hospital Medical School.

Mr MacGillivray, who is 40 years of age, was educated at Vale of Leven Academy, Alexandria, and the University of Glasgow He qualified in 1944 and was awarded a Gardiner research scholarship Later he became lecturer in midwifery at the University of Glasgow and senior registrar at the Royal Maternity Hospital In 1953 he was appointed lecturer in obstetrics and gynæcology at the University of Bristol and he took up his present appointment in 1955 He graduated M.D in 1953 and was elected F.R.C.O G last year His published work includes papers on renal, hepatic, adrenal and pituitary lesions in pregnancy and epidemiological and biochemical studies in pre-eclamptic toxæmia

Dr D G Evans, F R.S, director of the department of biological standards at the National Institute for Medical Research, has been appointed to the chair of bacteriology and immunology at the London School of Hygiene and Tropical Medicine

On Oct. 12 the degree of M.D was awarded to R. S Williams

At recent examinations for D P M. the following were successful

Joan Tugwell, H M. N Rees, Hilary Richards

University of Edinburgh

Dr G M Carstairs, director of the Medical Research Council Unit for Research on the Epidemiology of Psychiatric Illness, Tavistock Square, London, has been appointed to the chair of psychological medicine in succession to the late Prof Alexander Kennedy

Dr Carstairs, who is 45, was born in India where his father was a Church of Scotland missionary He was educated in Edinburgh at George Watson s College and the university, where he read arts as well as medicine and was medallist in fine art In 1941 he graduated M.B and after holding house-posts he served as a medical officer in the Royal Air Force in Europe and the Far East, mainly with No 3 (Fighter) Squadron with whom he learned to fly During the war he became interested in social anthropology, particularly in the influence of cultural environment on personality development After the war he was senior registrar at Warneford Hospital, Oxford. During 1948–49, with a Commonwealth Fund fellowship, he studied social anthropology under Dr Margaret Mead in New York in preparation for two years of field studies in primitive village communities in Rajputana These researches were published in his book *The Twice Born* (1957) Before taking up his present post in 1960 Dr Carstairs was assistant director of the M R C social psychiatric research unit and an honorary consultant at the Maudsley Hospital

Dr D M Weir has been appointed lecturer in bacteriology, and Mr J D O Loudon part-time lecturer in obstetrics and gynæcology

Royal College of Surgeons of England

The annual meeting of fellows and members is to be held on Wednesday, Dec. 7, at 3 30 P.M., at the College, Lincoln's Inn Fields, London, W C.2

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[1] See *Lancet*, Sept. 3 1960 p 535

Royal College of Obstetricians and Gynæcologists

At a meeting of the council on Nov 26, with Mr A C H Bell, the president, in the chair, Prof Derk Crichton (Durban, South Africa) was appointed the William Blair-Bell lecturer for 1961, and Prof C H G Macafee the William Meredith Fletcher Shaw lecturer Mr H H Francis was awarded a Bernhard Baron travelling scholarship, Dr Bruce Eton and Dr G A Humphreys Green-Armytage travelling scholarships, and Dr J S Scott the Edgar-Gentilli prize

The following were admitted to the membership

Mavis F Anderson, F W Van der Westhuizen

The diploma in obstetrics was awarded to the following

Robert Abendstern, E I Adam, Ezekiel Adewumi Bolaji Adenuga, J B Akingba, J M Allan, J G Allardice, A J R Anderson, J P Andrew, D J Annal Madhusudan Biharilal Atit, Sudha Madhusudan Atit, George Atkins S H Aynsworth, Judith M Babb, Clarice A Baker, D H Ball, Ann D Banister, Margaret Baron, Isabelle B Barrie P C Barrington, Anne C Bayley, M D Begley, D L Belcher S M Berger, A T Bevan, J S Bevan, J E Bewley, Beryl Beynon Suniti Kumar Bhattacharyya, A R Bingham Geoffrey Birchall, Anne W Birt Sybil Birtwistle, R B B Bishton, D H Black, J A Blecher, Henry Bodsworth, H F Bolton, M G Bradley, Barrie Breeze-Stringfellow, Beatrice M Brown, K A C Brown, Judith C H Bullen R A Bunting L J Burton Christine M Butler, P R Butler, K N Butteriss, W D Callum, I G Campbell, I G Carnegie Brown, R M Carson, P A Carter, R N Carter, J M Chadwick, Vimla Chaudhry, P J Chaudoir, I G Chisholm, R S Churchill, R G Clark, Daphne C K Clarke, Peter Cochrane, G F Cockings R H L Cole, Daniel Connan Alison R Coutts, D H G Cowie, Jane M Craig, W S R Craig, H E Cramp, Jane M Critchley, Matilda E Cuming J B Davis, R P Davis, Anne A N Day, W R Dean, Harvey Dexter, P N Dixon, Jeane B Donaldson, J A Driscoll J R E Edmondson-Jones, A J Ellison, A J H Ellison, David Emerson, William Erskine, Iain Esslemont, Beryl H Evans G R L Evans J F Farrall, C J Farrer, M J Feitelberg, Jean M Fell, P L Ferguson, M A Ferri, J A C Fisher, P G T Ford, D F Foster, William Foster, Patricia A J Freeman, R F R Gardner, I I Gaston, E E Genever, D M George E R Gibbons, Phyllis M Gibbons, Janet I Gibson, Sidney Ginsberg P J Gladders Selwyn Glick, J B Gnanapragasam, Alan Gooding, G T Gooding, R A Gould T R Gould, G S Graham, Colette C Green, Ronald Greenbaum P R Greenfield R A W Guthrie, Judith M Hall, M J Hall, S W D Hall T J Hall, A W Harris D F Harrison A S Hartt, Mehar Qamrul Hasan, Gerald Hass D A Hastings, J P Hawe, M J Hegarty R S Hickling J H Higgins F R Hilborne, D G W Hollands, J R Holliday, P S Hollingworth, J G Holmes Smith Marie K Housley, E G Hoyen Chung V P Hynes, Michael Ibberson, G D Ikedife E A Ikomi, D H Irvine, Alberta E Irwin, Teresiamura Jacob, P W James, I W Jamieson, Sadrudin Alibhai Janmohamed, D C Jeffery, D M Jenkins D L Jennings W A Johns, J K Johnson M L Johnson, P A Johnson, I N L Johnston, A J Jordan John Keane, Denis Keating, Trixie Kelly, Martin Kelvin N B Kirkland, Saramma Koshy Serge Kunstler, F K A Laing, W I Lamont, Marjorie M Langmuir, Osafo Lartey, C J N Lawson, D J Lawson P M Leary, J A S Lees, M M Lees, J E Leng P M Lenten, R B Levy, D W Lewis, H M Liegeois J P Lissenden, J R B Livingstone, J K Lloyd J O Lloyd-Jones, V J E D Lobo, Barbara A Lockley, R M Lodge K E Luckman M V McCabe, T N McCarthy, B W M Macartney, Jean L McColl, G C A MacDevitt J D Macdonald, R C Macfarlane, J P MacFaul R F McGann, J C McGrand, Helen R McKilligin J G McLaggan, W S S Maclay, Hugh Macmaster, D C McNeill, Stephen McPherson R L McRitchie, P D Maddocks B W Maitland, Valerie Major, Debabrata Mallik J W Maltby, Annamma Mammen, William Manton, J A Mathews, R D Mathias Hazel J Matthews, Thomas Mawdsley, R E May, Hamida Sultana Memon, Romola A Menezes G M Milne, R G Milne, Alison M Molyneaux, M W Moncrieff, P R Monk, K A M Moore M J Moore, G L Morgan J F Morris, K A A Mourin E S Mucklow, I S Muir Subimal Mukerjee, H D R Munro, Helen M G Murray Mya Mya E A Neville, Margaret P Newton, J D Nicholas J B Nichols Jennifer M Nixon, J B Nuttall P P S Nylander F A Olapade Zubeda Osman Alexander Osmond, J D Owen Glenys R Packer M J Page D J Palmer Indu Fakirbhai Patel, A W Patterson K R Peel M G Peters J A Phelan, F S Plumpton Margaret D Power Audrey J N Price, H V Price, J D Price J L Price D J Prosser, H S Radden Tadeusz Radomski, P G Rae, P B Read B L E C Reedy, Shirley J Richards Margaret Richardson, A E Ridley R M Ridsdill Smith, J A Rigby Catherine O L Rimington J K Roberts, Irene J Robertson, Moira C Robertson R W K Rogers J N Roskilly, K W Rowden, W N T Roy Elizabeth M Russell, J L Russell, J G Russell, Lorna J Rust Naomi J Sage S S Sanders, I W H Scott, M D Scott, A H Sears, M S Seltzer, C R Sexton Jean Shackleton, H J Shapiro, E A Shaw F D Skerrett J O Sibthorpe R I D Simpson R O Skinner, E C Smart Frederick Smith R C Smith J K Snell, Christine A Snodgrass J B Sorapure D F Spencer, G M Steiner W J Stephen B J Stevenson W B Stewart Sheila M Strachan, Mylvaganam Sundaralingam H W Sutherland G H Swapp R M R Taylor, R W Taylor, William Taylor Henry Teed I P Thew P S Thomas Andrew Thomson Freda M Tomlinson Elisabeth A Tooth John Tudor Lorna S Vethavanam J C Voigt Ruth E H Wainwright, Pamela Walton J T Ward Joyce Warner, M S Warwick, P H Waterfield R R Watkin R A Watkins, A J Watson A B Watson Dorothy A Watson Anne H White James Wightman, Anne M Wigley Aled Williams G L Williams Barbara J Willmer Derek Wilson J M Wilson Marie B Wilson C E R Winer G B Wolloff J M Woodhead, Michael Woodliff R G Wrangham Maureen L Wyllie H N Young

Treacher Collins Prize

The subject chosen for the next award of this essay prize (£100) which is offered triennially by the Ophthalmological Society of the United Kingdom, is demyelination and the eye The closing date for submitting essays is Dec 31, 1962 Further particulars may be had from the hon secretary of the society, 17, Lincoln's Inn Fields, London, W C 2

British Medical Association

On Thursday, Dec 15, at 5 30 P M, at B M A House, Tavistock Square, London, W C 1, Mr Henry Osmond-Clarke will open a lecture-discussion on fractures around the wrist

British Association of Physical Medicine

A meeting of this Association will be held on Friday, April 21, at the Royal National Orthopædic Hospital, Stanmore, and on Saturday, April 22, at Westminster Hospital, London, S W 1

Royal Society of Edinburgh

David Anderson-Berry Medal and prize (£100)—An award will be made in 1961 for recent work on the effects of X rays and other forms of radiation on living tissues Applications for the prize, or proposals on behalf of others, must be in the hands of the general secretary of the society, 22, George Street, Edinburgh, 2, Scotland, not later than March 31

Living Conditions, Health, and Economic Development

The International Medical Association for the Study of Living Conditions and Health will hold a conference on this subject from Sept 29 to Oct 1 at St Vincent, Aosta Valley near Turin, Italy Further particulars may be had from the general secretary of the Association, Burggasse 71/I/6, Vienna 7, Austria

Central Council for Health Education

The annual conference of this Council will be held on Thursday, Jan 26, at 10 30 A M, at the National Film Theatre, London, S E 1 The theme of the conference will be the Road to Maturity and the speakers will include Dr David Stafford-Clark and Dr M S Harvey Further particulars may be had from the medical director of the Council, Tavistock House North, London, W C 1

International Congress of Neurology

This congress will be held from Sept 10 to 15 in Rome Subjects to be included in the programme are neurological disorders in porphyria, phenylketonuria, and galactosuria, brain disturbances associated with cardiopulmonary disorders, and aphasia On Sunday, Sept 10, a symposium of neurological genetics will be held in conjunction with the international conference of genetics Further particulars may be had from Dr G Alema, Viale dell'Universita, 30, Rome

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Sir Robert Platt, P R C P, has been elected to the honorary fellowship of the American College of Physicians This will be conferred on him in May when he visits the United States to give the Lilly lecture

Dr G W Corner, FOR MEM R S, historian of the Rockefeller Institute, New York, and director emeritus, department of embryology of the Carnegie Institution of Washington, has been appointed executive officer of the American Philosophical Society, Philadelphia He will retain a connection with the Rockefeller Institute as visiting professor

On Monday, Dec 5, at 8 15 P M, at the Marlborough Day Hospital, 38, Marlborough Place, London, N W 8, Dr Joshua Bierer will speak on the Future of the Mental Health Services in Great Britain

A meeting of the Biochemical Society will be held on Friday, Dec 16, at 10 10 A M, at Guy s Hospital Medical School, London, S E 1

A meeting of the medical and scientific section of the British Diabetic Association will be held at University College Hospital, London, W C 1, on Friday and Saturday, April 7 and 8

Appointments

CLARK E M, M R C S, D M T & H, assistant M O H, Nottingham
DALLACHY RUSSELL, M B Glasg, consultant pathologist, West Cumberland group of hospitals
MEEHAN MARY T, M B, N U I, school M O, North Riding of Yorkshire

Middlesex County Council

KLASSNIK B, M B, assistant M O, Tottenham and Hornsey
NICHOLLS JOAN H, M B Lond, assistant M O, Tottenham and Hornsey
SETHI G S, M B Punjab, D T M & H, D P H, assistant M O, Tottenham and Hornsey

The Lancet · Saturday 10 December 1960

THE DUMPING SYNDROME
CLINICAL AND RADIOLOGICAL ASPECTS*

H T Cox
M.A , M.D Cantab , F R.C S.E
CONSULTANT SURGEON,
WITHINGTON AND WYTHENSHAWE HOSPITALS, MANCHESTER

W R. Allan
B.A. Oxon., M B Edin , F R.C S , F R C S.E
SURGICAL REGISTRAR, WITHINGTON HOSPITAL, MANCHESTER

This paper is based on a study of the dumping attacks in 500 patients who had had an elective gastric operation in the past six years

It deals with the clinical aspects of the dumping attacks which may follow the ingestion of certain normal foods and with the radiological appearances during them We have not, as other investigators have done, used hypertonic glucose to produce symptoms resembling those of the dumping attack.

Clinical Aspects

Classification

Patients with dumping attacks can be divided into two main groups in one, the attack is brought on by a large meal, in the other by particular foods There is a further group in which the symptoms though resembling those of the dumping attack, have no well-defined relation to the size or nature of the meal Most of these symptoms are probably those of hypoglycæmia

Choice of Patients for Investigation

The disadvantage of investigating dumping attacks after a large meal is that it may include some constituent, of which the patient and the investigator are unaware, that initiates dumping, quite apart from the effect of distension We have, therefore, confined this investigation to patients whose attacks of dumping are brought on by particular foods Cox and Kerr (1957) showed that there was, after 75% partial gastrectomy without vagotomy, a definite selective impairment of digestion for milk, milk puddings, eggs, fatty foods, pastries, and chocolates These foods produce either a dumping attack or symptoms of dyspepsia

Reproduction of Natural Dumping Attacks

Patients who gave a clear history of dumping attacks brought on by particular foods were invited to attend as outpatients, and were given these foods Two points are important firstly, the attempt to reproduce the attack should be carried out in a room at or above average ward-temperature, secondly, the patient must not lie down after eating but should walk slowly up and down

Clinical Picture

We have reproduced fifteen attacks of dumping during the past six years, and these notes are based on our observations

The outstanding symptom of the dumping attack is profound weakness, usually associated with light-headedness All other symptoms are relatively minor The weakness is general, but may especially affect the legs

It has been described by the patient as " feeling awful ", " as if all the use had drained out of me ", and " as if I was going to die "

During a severe attack of dumping, the patient is totally incapacitated If he continues to walk during the attack, he staggers and falls to the ground The patient usually lies down, not to relieve the attack, but simply because he cannot stand up

The vertigo of which the patient is said to complain, is not a true vertigo, but a sensation of being light-headed

Most severe attacks include ocular symptoms These have been variously described by the patient as an inability to focus, a blurring of vision, the presence of a dark shadow in front of the object looked at, or a sensation of seeing things as if far away A patient was given a newspaper to read She was quite unable to read the small print, but could just read the large headlines

Both posture and exercise can determine whether the patient has an attack

(1) An attempt was made to take superficial and deep temperatures on a few patients during the dumping attack. This meant that they had to lie flat When in this position, no major attack of dumping could be reproduced and the patients experienced only a mild and transient weakness not sufficiently severe to be worth investigation These patients had recently had major attacks of dumping when standing or walking after taking similar foods

(2) A patient said that his dumping attacks especially after sweet fatty foods, could always be brought on by walking after the meal, but could be delayed or prevented by lying down

(3) In another patient, during radiological examination, a severe attack of dumping necessitated his lying horizontally on the X-ray table. After the attack had passed off, the head end of the table was slowly raised When it reached 45°, the attack recurred with its original intensity, and the table had to be replaced in the horizontal position

(4) A patient had a severe attack of dumping five minutes after a mixture of hot milk and egg, taken standing up and followed by the usual slow walking Three weeks later this mixture, in the same amount and at the same temperature, but given when she was lying down, produced no attack of dumping during a period of thirty minutes She then walked up and down, and within two minutes she had an attack as severe as her previous one

Recumbency delays or prevents the onset of the dumping attack, a vertical position does the opposite Getting up after lying down brings on the attack with its original intensity

The interval between taking particular foods and the onset of the dumping attack has varied from two minutes to twenty minutes in our series, when the meal has been followed by slow walking After a hot-milk-and-egg mixture, sweetened or unsweetened, the interval is usually three to five minutes Among the factors which affect this interval are (1) the temperature of the food, hot milk producing an earlier attack than cold, (2) the temperature of the surroundings, heat again accelerating the attack, and (3) a diminishing tendency to dumping attacks

There is no pallor during the attack. Most patients become drowsy and irritable when the attack is passing off

Vomiting was noted once only a small amount of bile being returned No diarrhœa has occurred in relation to the dumping attack.

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* Based on a presidential address before the section of surgery, Manchester Medical Society, October, 1958

Blood-pressure during attacks did not fall in a way that could account for the symptoms, in fact, there was often a slight rise

Radiological Examination

6 patients (see table) were X-rayed during natural dumping attacks

The foods responsible for the attacks were

Milk, with one beaten-up egg (2 cases), milk, with one beaten-up egg and one teaspoon of sugar (1), and Horlicks, with one beaten-up egg and one teaspoon of sugar (3)

All these foods were given hot The volume was 8 oz (227 ml), except for a patient in the Horlicks group who took only 5 oz (142 ml) The average interval between giving these foods and the onset of the attack was three minutes the shortest interval was two, and the longest, five minutes

In 4 of these 6 patients, the attack was so incapacitating that they were unable to continue standing during the examination The other 2 attacks were of moderate severity

Procedure

A preliminary examination after a barium swallow outlined the gastric stump, stoma, duodenum or jejunum (according to the type of gastric operation) and showed the rate of emptying

The patient, having eaten the food responsible for dumping, walked slowly up and down He was re-screened at intervals and on the first symptoms of the attack, a complete radiological examination was done If necessary, the patient was given further swallows of barium

Immediately the attack had passed off, more films were taken after further barium swallows (if necessary)

Controls

Two sets of controls were used In the first, 3 of the 6 patients were given 8 oz (227 ml) of hot tea without sugar or milk after the dumping attack had passed off In the second, 4 additional patients were given 8 oz (227 ml) of hot milk, with one beaten-up egg and one teaspoonful of sugar This mixture had previously caused dumping attacks in all 4 patients, but these foods no longer produced symptoms

DETAILS OF PATIENTS IN WHOM DUMPING ATTACKS WERE OBSERVED RADIOLOGICALLY

Operation	Diagnosis	Sex	Age	Interval between operation and radiological examination of dumping attacks (years)
P G (S)	G U	M	54	1
P G	G U and D U	F	45	4
P G	D U	M	33	4
Vagotomy and P G	Anastomatic ulcer	F	39	4
Vagotomy and P G	D U	F	15	3
P G	D U	M	36	7

P G = 75% partial gastrectomy, antecolic with spur, S = Schoemaker partial gastrectomy, G U and D U = chronic gastric and chronic duodenal ulcer

Results

The preliminary examination in all 6 patients showed a normal outline of gastric stump, stoma, and upper jejunum or duodenum, with the usual rapid emptying and hyperperistalsis

The screening in the 4 patients with severe attacks of dumping showed complete stasis and dilatation, affecting the gastric remnant, duodenum, and jejunum. All forward movement ceased The appearance and disappearance of these changes coincided with the start and finish of the dumping attack 2 patients with less severe attacks showed similar but lesser changes All films taken immediately after the attack showed complete return to the normal emptying and hyperperistalsis shown in the preliminary examination (figs 1 and 2)

The first patient was X-rayed by Dr J Blair Hartley, who remarked that the findings were those to be expected from X-raying a body on the postmortem table Whether the patient was viewed erect, horizontally, or in any oblique position, there was absolute stasis, apart from a small trickle of barium into adjacent coils on palpation or immediately after a change in

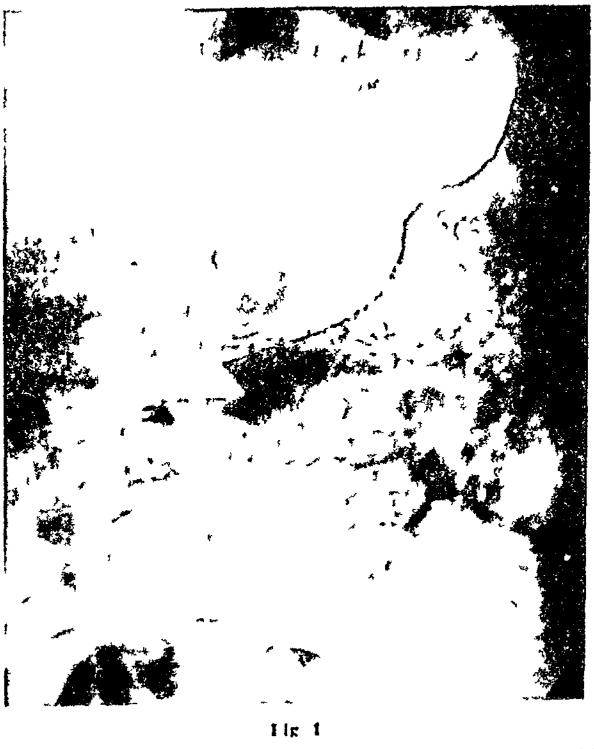

Fig 1

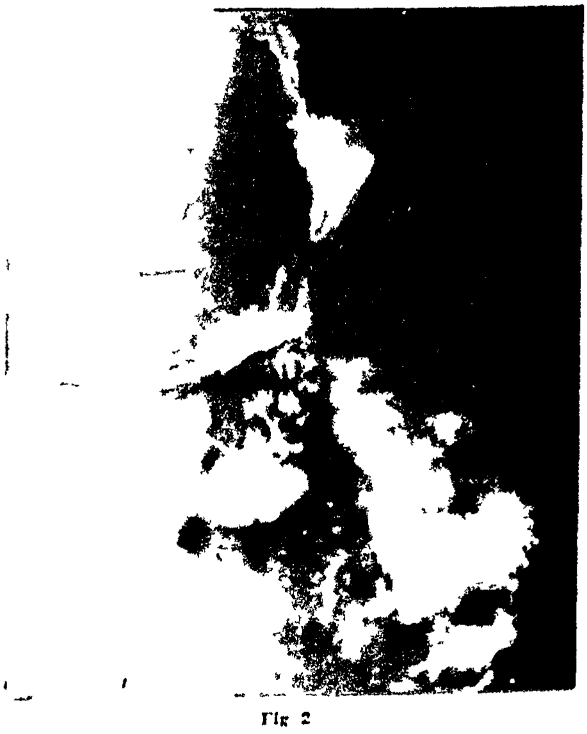

Fig 2

Fig 1—Schoemaker partial gastrectomy for gastric ulcer Film during dumping attack thirty minutes after one mouthful of Micropaque at onset of attack Stasis and dilatation in remaining portion of stomach and in duodenum and jejunum

Fig 2—Control film after attack had passed taken immediately after one mouthful of micropaque Complete return to normal

position There were no signs of increased fluid in the gut—that is, there was no dilution of the contrast medium, no blurring of the mucosal pattern, and no fluid levels

In the 3 controls given hot tea without milk or sugar after the attack had passed off, the active peristalsis demonstrated in the preliminary film was unchanged The four patients given hot milk with an egg and sugar without producing any symptoms of dumping also showed no change in the active peristalsis

Discussion

Our findings differ from those of previous workers in two essential points—the absence of motor activity and the lack of evidence of increased fluid in the gut during the attack

Glazebrook and Welbourn (1952) described increased motor activity in the jejunum at the time of dumping symptoms Amdrup et al (1958) demonstrated increased motor activity and signs of increased fluid in the gut during dumping symptoms All these investigators used a 50% glucose solution to produce the symptoms Such symptoms can be reproduced by hypertonic glucose (Machella 1949), and there seems no doubt that motor activity is increased, perhaps with signs of increased fluid in the gut, when symptoms like those of dumping are reproduced in this way We do not know, however, whether the cause and mechanism of these symptoms are the same as those of the natural dumping attack induced by normal foods We have reproduced the natural dumping attack after certain normal foods, and our findings are based on the validity of natural phenomena There is stasis, dilatation, and no peristalsis in the gastric remnant, duodenum, and jejunum during the natural dumping attack that follows certain normal foods There is no evidence of increased fluid in the gut

Summary

Dumping attacks after subtotal gastrectomy may be brought on by eating specific foods—milk, milk puddings, eggs, fatty foods, chocolates, and pastries The outstanding symptoms of an attack are profound weakness and a feeling of light-headedness A severe attack may totally incapacitate the patient Walking, especially in a warm atmosphere, and taking foods that are hot, increases the severity of the attack

Radiological examination during attacks shows stasis, dilatation and no peristalsis, in the gastric remnant, duodenum, and jejunum The appearance and disappearance of these changes coincided with the start and finish of the attack The worse the attack, the more striking were these changes

Those workers who used 50% glucose solutions to reproduce symptoms like those of dumping, suggested that hyperperistalsis is present in a natural dumping attack Our findings were quite unexpected, and demonstrate the importance of investigating the natural dumping attack that follows normal food

It is a pleasure to record our thanks to Dr J Blair Hartlev and to Dr J F Doherty for carrying out the radiological examinations, and to the South Manchester Hospital Management Committee for financial assistance

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Cox, H T, Kerr D F (1957) *Brit med J* i 1211

Glazebrook A J, Welbourn R B (1952) *Brit J Surg* 40 111

Machella T E (1949) *Ann Surg* 130, 145

INTRINSIC FACTOR ANTIBODY IN SERUM FROM PATIENTS WITH PERNICIOUS ANÆMIA

MICHAEL SCHWARTZ
M D Copenhagen
MEDICAL DEPARTMENT B AND CENTRAL LABORATORY, BISPEBJERG HOSPITAL, COPENHAGEN, DENMARK *

ANTIBODY to Castle's intrinsic factor (I F) was demonstrated in 1958 by Taylor and Morton in serum from rabbits immunised with either hog or human I F The antibody, or at any rate an I F-inhibiting substance, was demonstrated in fæcal-excretion experiments on patients with pernicious anæmia in whom immune serum from the rabbits inhibited the effect of I F, both hog and human

Faced with the problem of acquired resistance to I F in patients with pernicious anæmia treated orally, I looked for I F antibody and found it in serum from several of these patients (Schwartz 1958) At the same time, this I F-inhibiting substance alone could not explain the acquired resistance to I F, since the I F antibody was also present in patients with pernicious anæmia treated by mouth, who did not have intestinal block

The presence of an I F-inhibiting substance (antibody) in the serum of patients with orally treated pernicious anæmia has been confirmed by Lowenstein et al (1958) and by Berlin (1959) Most recently, Taylor (1959) has found I F antibody in 9 out of 19 patients either treated by parenteral administration, or else untreated

During the past 2 years, I have examined a large number of sera for I F antibody These sera were obtained from patients with pernicious anæmia, and from normal subjects In addition, investigations have been made to elucidate the nature and mode of action of the presumed antibody

Methods

The methods used were essentially the same as reported earlier (Schwartz 1958)

^{58}Co vitamin B_{12} was used in most investigations All the hog pyloric mucosa was from the same batch The Schilling (urinary excretion) test was used throughout 0 5 µg ^{58}Co-B_{12} was administered by mouth and, $1^1/_2$ hours later, 1 mg unlabelled B_{12} intramuscularly The test for antibody against

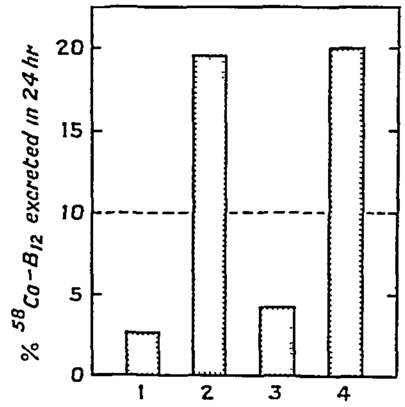

Fig 1—Urinary excretion in four Schilling tests in a patient with pernicious anæmia

(1) Without I F, (2) with I F (100 mg hog pyloric mucosa), (3) with I F plus 50 ml serum with I F antibody, and (4) with I F plus 50 ml normal serum Dotted line = lower limit of normal

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* Present address Medical Department F, Copenhagen County Hospital, Glostrup, Denmark

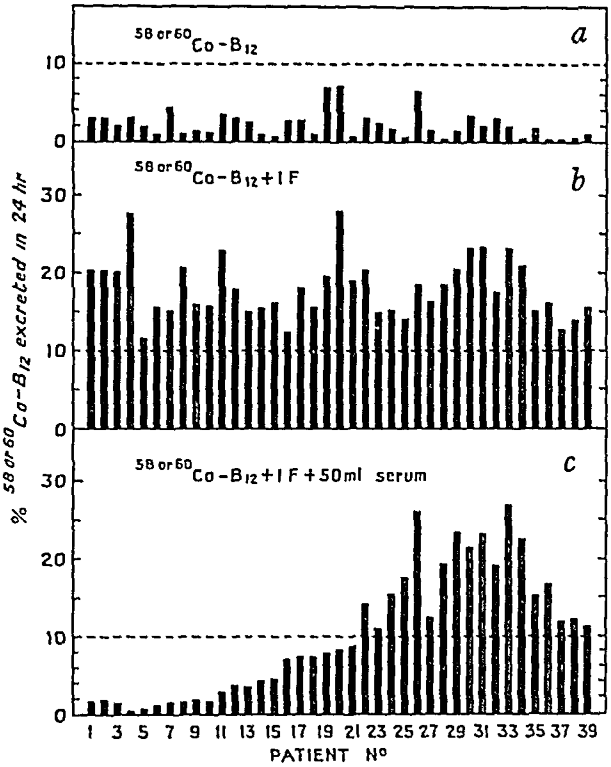


Fig 2—Urinary excretion in Schilling test

(*a*) Without I F, (*b*) with 100 mg hog pyloric mucosa, and (*c*) with 100 mg hog pyloric mucosa plus 50 ml serum from 39 patients with pernicious anæmia treated orally with vitamin B$_{12}$ plus hog pyloric mucosa Figures are percentages of administered ^{58}Co-B$_{12}$ or ^{60}Co-B$_{12}$ excreted in 24 hours

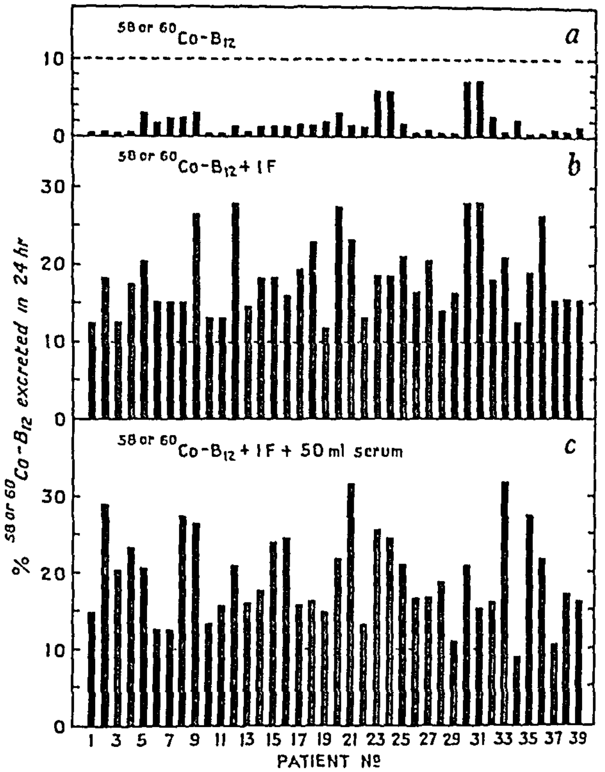


Fig 3—Urinary excretion in Schilling test

(*a*) Without I F, (*b*) with 100 mg hog pyloric mucosa, and (*c*) with 100 mg hog pyloric mucosa plus 50 ml serum from 39 normal persons Figures are percentages of administered ^{58}Co B$_{12}$ excreted in 24 hours

I F was carried out by mixing 100 mg hog pyloric mucosa with a small amount of water, and then with 50 ml serum at room temperature 10 minutes later the mixture was given orally with the test dose of ^{58}Co-B$_{12}$ Fig 1 shows the standard procedure and the result of the urinary excretion tests (U E T) using a serum with, and a serum without, I F antibody

Results

The object was to find an explanation of the iatrogenic block in vitamin-B$_{12}$ absorption which often occurs in long-term treatment with oral preparations of vitamin B$_{12}$ plus hog pyloric mucosa ('Bendogen', 'Cycoplex') (Schwartz et al 1957, 1958, Killander 1957, Lowenstein et al 1957, Stokes and Pitney 1958) I F antibody was found in the preliminary study (Schwartz 1958), and in a larger series this finding was confirmed Fig 2 gives the result of looking for I F antibody in 39 patients treated by mouth with preparations of vitamin B$_{12}$ plus hog pyloric mucosa for more than a year It will be seen that I F antibody was found in more than half the patients, often in such quantity that the effect of 100 mg hog pyloric mucosa was abolished

In serum from normal persons, such an I F-inhibiting action could not be detected Fig 3 gives the result of the study in 39 normal persons in none of whom did the administration of 50 ml serum affect the I F activity

It has already been shown (Schwartz et al 1958) that pernicious-anæmia patients treated orally by crude stomach preparations either acquired no resistance to hog I F, or else did so to a slight extent only Sera from a group of patients treated (often for decades) exclusively by this method, proved to contain I F antibody about as often as sera from patients treated with vitamin B$_{12}$ plus hog pyloric mucosa (fig 4) A feature common to these two groups is that for years they have been receiving heterologous I F

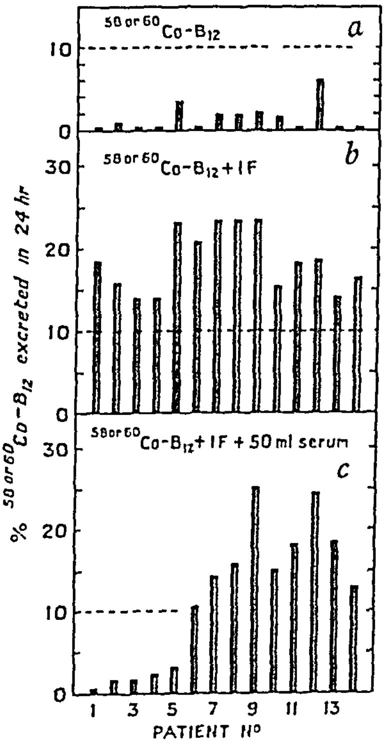


Fig 4—Urinary excretion in Schilling test

(*a*) Without I F, (*b*) with 100 m[illegible] hog pyloric mucosa and (*c*) with 100 mg hog pyloric mucosa plus 50 ml serum from 11 patie[illegible] with pernicious anæmia treated orally with a crude stomach preparation Figures are percentages of administered ^{58}Co B$_{12}$ or ^{60}Co B$_{12}$ excreted in 24 hours

Fig 5 gives the result of an investigation of 33 previously untreated patients with pernicious anæmia In a little over 25%, antibody was detected in the serum

5 patients treated exclusively by injections did not have I F antibody

Sera from 91 patients with pernicious anæmia were studied I F antibody was found in 36, most of whom had been treated orally with hog I F, but it was also present in several with untreated disease

The quantity (50 ml) of serum used in all these and earlier experiments was chosen arbitrarily The technique

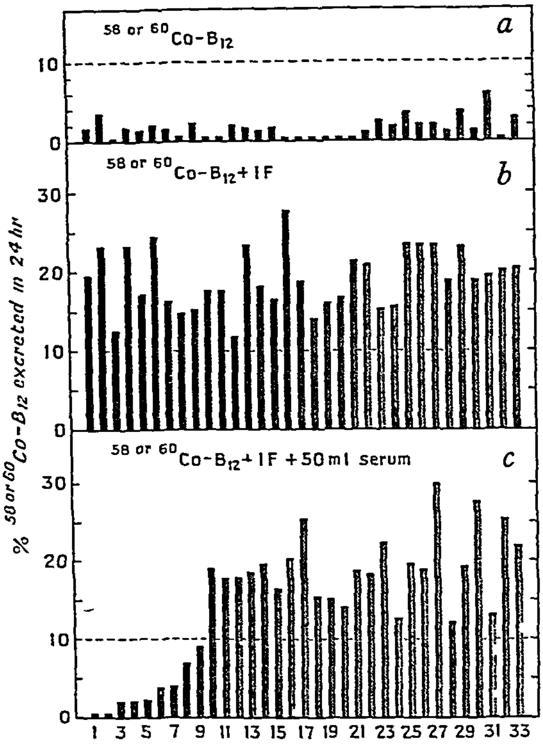


Fig 5—Urinary excretion in Schilling test

(*a*) Without I F, (*b*) with 100 mg hog pyloric mucosa, and (*c*) with 100 mg pyloric mucosa plus 50 ml serum from 33 patients with untreated pernicious anæmia Figures are percentages of administered ^{5} Co-B$_{12}$ or ^{60}Co-B$_{1}$ excreted in 24 hours

allows, to some extent, titration of the quantity of antibody, the amount of I F (antigen) being kept constant, and the amount of serum (antibody) varied

Fig 6 shows such a titration, using serum from 3 different patients 5 ml of the most active serum contained sufficient antibody to abolish the effect of 100 mg hog pyloric mucosa, which normally affords an almost maximal absorption effect The middle curve shows the I F -inhibiting activity of a serum in a case where the patient (with untreated pernicious anæmia) served as the test subject

Hog I F had been used in all the experiments so far described but the I F antibody evidently acts upon I F from other animal species

Fig 7 presents the result of experiments, using I F of human origin (desiccated, degreased, crude fundus of a human stomach), showing that the I F antibody acts upon human I F As is apparent from fig 8, it also inhibits rat I F

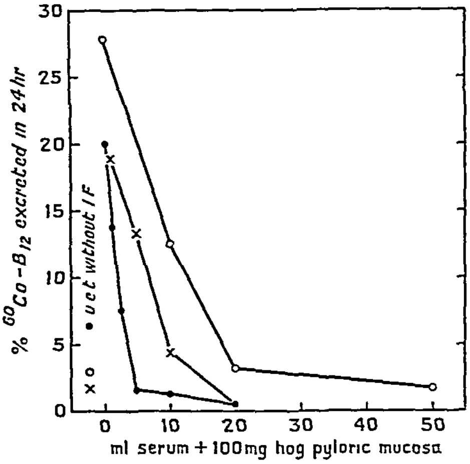


Fig 6—Urinary excretion in Schilling test

With 100 mg hog pyloric mucosa plus varying amounts of serum from 3 pernicious anæmia patients with I F antibody Each curve represents 1 patient Figures are percentages of administered ^{60}Co-B$_{1}$ excreted in 24 hours

The I F antibody is also effective against human I F in vivo Fig 9 shows 2 patients, both of whom had normal B$_{12}$ absorption, one with achlorhydria and the other without In the achlorhydric patient, the I F antibody was active against hog I F and there was as well an almost complete inhibition of the patient's own I F In the patient with free hydrochloric acid in the stomach, the I F antibody was evidently inactive.

Discussion

It was soon fairly evident that the I F antibody did not account for the treatment induced block in intestinal absorption, if only because no correlation could be found between blockade and presence of antibody However attractive this hypothesis might be, it seems to have been completely disproved by the finding that the antibody is not species-specific and that it may be present also in untreated pernicious anæmia

There are several good reasons for assuming that we are dealing with a true antibody of immune nature

1 Taylor (1958) found that I F possessed antigenic

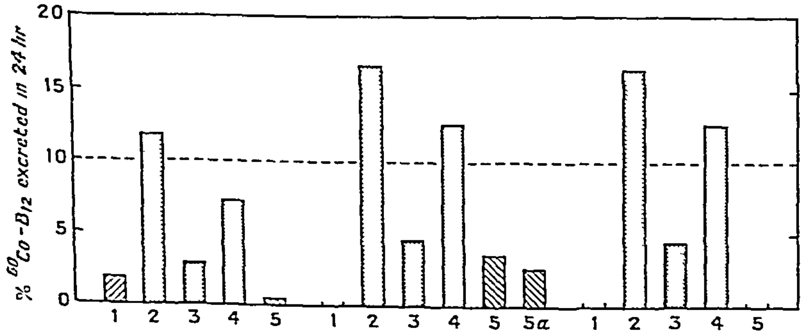


Fig 7—Urinary excretion in Schilling test

(1) Without I F, (2) with 100 mg hog pyloric mucosa, (3) with 100 mg hog pyloric mucosa plus 50 ml serum with I F antibody, (4) with human I F (300 mg desiccated human fundus), and (5) with human I F plus 50 ml. serum with I F antibody (5a—repeat of 5)

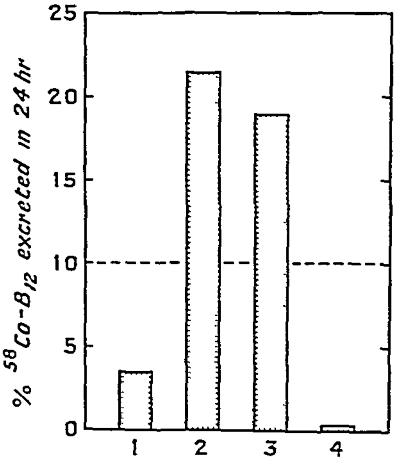


Fig 8—Urinary excretion in Schilling test

(1) Without I F, (2) with hog I F (100 mg hog pyloric mucosa), (3) with rat I F (50 ml rat gastric juice), and (4) with rat I F plus 10 ml serum from patient with I F antibody Figures are percentages of administered ^{58}Co-B$_{12}$ excreted in 24 hours

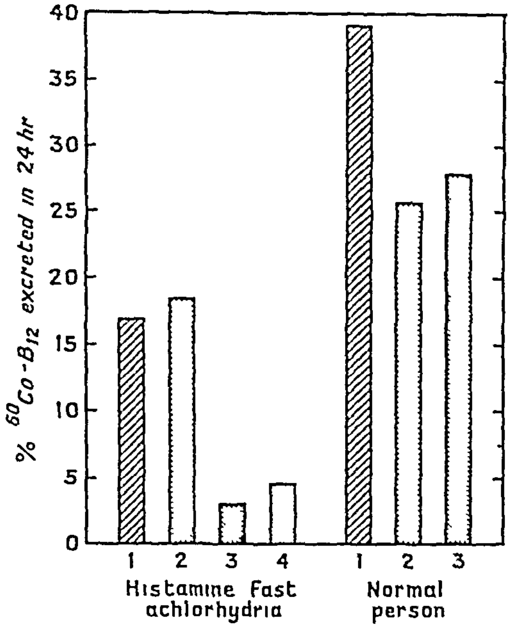


Fig 9—Urinary excretion in Schilling test in 2 patients without pernicious anæmia

(1) Without I F, (2) with hog I F, (3) with hog I F plus 10 ml serum with I F antibody, and (4) with 10 ml serum only (patient with achlorhydria) *Figures are percentages of administered* ^{60}Co-B$_{12}$ excreted in 24 hours

properties, since rabbits could be immunised by I F, producing an antibody abolishing its most characteristic property—namely, the ability to promote the absorption of vitamin B$_{12}$

2 The active factor in serum possessing I F-inhibiting action is localised to the globulin fraction as might be expected of an antibody (fig 10)

3 Hydrocortisone treatment of patients with I F antibody in the serum may result in disappearance of the antibody—at least temporarily (Taylor 1959) This disappearance of the antibody-content during treatment with a corticosteroid strongly implies that it is an antibody of immune nature

The demonstration in vitro of a reaction between the hypothetical antibody and the corresponding antigen (I F) would be an even more cogent argument that the substance is a true antibody

Some of my sera with I F antibody, as shown by the method I have described, were investigated by Taylor with Coon's technique using fluorescein labelling of the antibody, and human stomach as antigen The results were not conclusive

Lowenstein et al (1958) have described a method for demonstrating I F antibody, using erythrocytes to which hog I F had been bound by *bis*diazobenzidine Agglutination of the treated erythrocytes takes place in the presence of antibody Lowenstein et al found I F antibodies in serum from rabbits immunised with hog I F, and in the sera of some patients with pernicious anæmia, orally treated, and refractory to hog I F preparations

By a modified Boyden technique, Latner (1959) studied a number of sera from patients with pernicious anæmia He states that the results were highly suggestive, but does not give further details Using his tanned-red-cell (T R C) technique, Boyden examined several sera from my patients Out of 42 sera studied by my technique as well as his own, 28 gave the same result with both methods (14 being positive and 14 negative), but in 14 instances the two methods gave different results Those sera which gave the higher titre with the U E T method also gave a stronger positive reaction with Boyden's T R C technique These investigations are being continued

The result of these various demonstrations, in vitro, of I F antibody must be taken as an indication that it is of

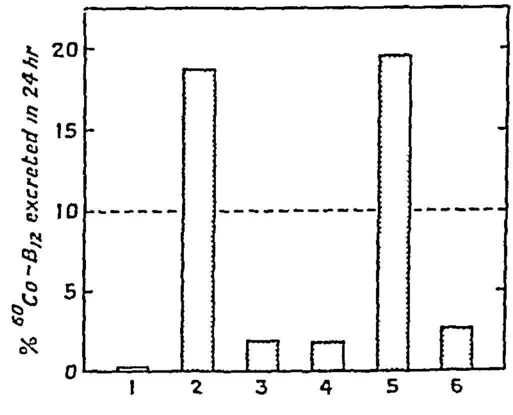


Fig 10—Urinary excretion in Schilling test

(1) Without I F, (2) with 100 mg hog I F, (3) with 20 ml serum with I F antibody, and with proteins in serum—total (4) and separated into albumin (5) and globulin (6) fractions Figures are percentages of administered ^{60}Co-B$_{12}$ excreted in 24 hours

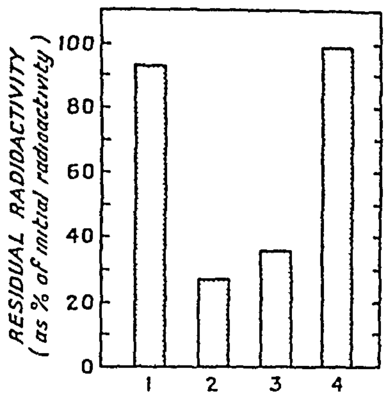
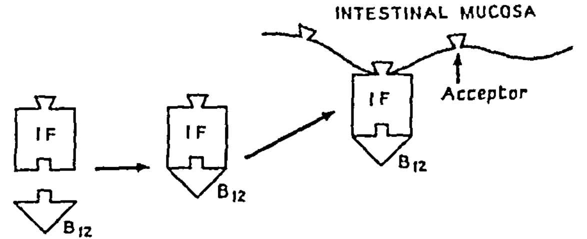
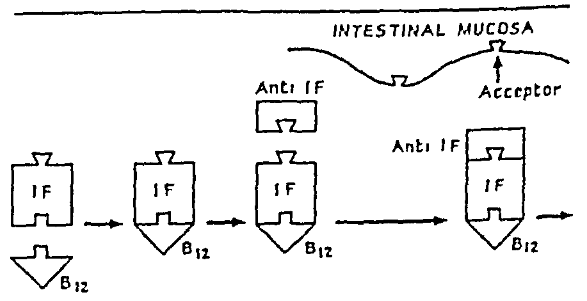


Fig 11—Effect of I F antibody on binding between ^{58}Co vitamin B$_{12}$ and hog pyloric mucosa

0 5 μg ^{58}Co-B$_{12}$ was mixed with (1) I F (100 mg hog pyloric mucosa) and water, (2) water, (3) serum with I F antibody, and (4) I F plus serum with I F antibody Each mixture was dialysed for 16 hours against tap water and the remaining radioactivity in per cent of the original was measured



Normal absorption of vitamin B12



Hypothetic effect of IF antibody on absorption of vitamin B12

Fig 12—Absorption of vitamin B$_{12}$—normal and in presence of I F antibody

true immune nature Improvements in the red-cell agglutination methods would be extremely helpful in the continued studies

Effect of the I F Antibody

The mode of action of the I F antibody is obscure, since the mode of action of the I F itself has not been definitely elucidated Possibly, further knowledge of the I F may be obtained through the antibody We know that I F is necessary for transporting vitamin B_{12} in sufficient amounts from the intestinal lumen to the intestinal wall (and possibly farther afield in the body) How the absorption of vitamin B_{12} is effected by the I F is unknown, but it is assumed that the mucosa of the small intestine possesses a specific acceptor capable of "catching" B_{12} plus I F (Glass et al 1954)

All I F preparations possess a marked B_{12}-binding property Preparations possessing I F activity without B_{12}-binding properties are not known

The effect of the I F antibody might be directed either towards the binding between B_{12} and I F, or towards the binding between the combined product B_{12} plus I F and the (hypothetical) intestinal acceptor

The first possibility is not likely From fig 11 it may be seen that in vitro the antibody does not prevent the binding between B_{12} and I F, and that it is not itself bound to B_{12} The second—namely, that the I F antibody prevents I F plus B_{12} from reacting with the specific acceptor of the small intestine—is more probable In fig 12 an attempt is made to illustrate this graphically

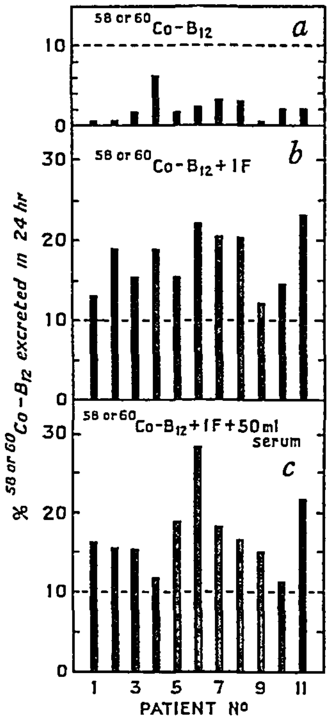


Fig 13—Urinary excretion in Schilling test

(*a*) Without I F, (*b*) with 100 mg hog pyloric mucosa, and (*c*) with 100 mg hog pyloric mucosa plus 50 ml serum from 11 patients with partial gastrectomy and defective I F production Figures are percentages of administered ^{58}Co-B_{12} or ^{60}Co-B_{12} excreted in 24 hours

Pernicious Anæmia as an Autoimmune Disease

Since the antibody to I F is demonstrable in the blood of patients with untreated pernicious anæmia, it probably arises from autoimmunisation Pernicious anæmia, in some cases at least, may be an autoimmune disease, as suggested by Taylor (1959) The reason the antibody is much more common in patients with pernicious anæmia, treated orally for some length of time, than in untreated patients could be that the long-term treatment with I F might raise a very low antibody titre to measurable values in some of the cases

Whether the autoimmunisation occurs because of, and at the same time as, the destruction of I F-producing cells (by gastritis, for example) or whether autoimmunisation is primary, the antibody being formed first (for some unknown reason) and then reacting with the I F-producing cells, must so far be pure speculation Recently, Siurala et al (1960) demonstrated major or minor I F deficiency in a group of patients with severe atrophic gastritis They emphasise that clinically some of these patients cannot be distinguished from those with pernicious anæmia Investigations of sera from such patients for I F antibody would be of great interest

A deficiency of I F is often found after partial gastrectomy (Lous and Schwartz 1959) In such cases, the I F deficiency is usually iatrogenic, and, theoretically, the patients should seldom if ever have any I F antibody Studying 11 patients with I F deficiency after partial gastrectomy, I did not find I F antibody in any case (fig 13), but no definite conclusion can be drawn until a larger number of sera have been studied

Summary

Sera from 91 patients with pernicious anæmia were studied for antibody to intrinsic factor (I F) This antibody was found in 36 patients, mainly those treated orally for some time, and also in several patients with untreated pernicious anæmia Sera from 39 normal persons did not contain I F antibody

The antibody is not species-specific, because it acts upon I F from man, hog, and rat It does not appear to be related to acquired resistance to hog I F

It is a true antibody, localised to the globulin fraction in the serum, and it is demonstrable in vitro It seems to be directed against that part of the I F molecule which is necessary for B_{12} absorption

The antibody may be characterised as an autoimmune substance, and so there is a possibility that pernicious anæmia may, in some cases, be an autoimmune disease

I wish to thank Dr S Boyden, Tuberculosis Immunisation Research Centre, Copenhagen, for performing tests for antibody with tanned red cells, and Mrs B Moller Petersen for valuable technical help The hog pyloric mucosa was supplied by Meco-Dumex, Ltd, Copenhagen

This work was supported by grants from Statens Videnskabsfond, University of Copenhagen, and King Christian X's Fund

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"Today we are being confronted with specimens that are either very small or in which the lesions are slight or minimal Under these new conditions it may well be that microscopic diagnosis may not have the same degree of validity and reliability that it has for the more usual large biopsy specimen taken after the disease process has become well established it is necessary that we keep clearly in mind the chief purpose of doing a biopsy which is to collect as objectively as possible the histopathologic evidence of disease and then to evaluate this evidence in the light of other evidence available about the patient's illness Objectivity in making histopathologic diagnoses and careful and honest correlation with the subsequent clinical course of the patient are proved ways of adding to knowledge that we should not lightly discard"—Prof WILLIAM B WARTMAN, M D, *Arch intern Med* 1960, 106, 603

ASYMPTOMATIC HYPERPARATHYROIDISM

MARY G MCGEOWN
M D , Ph D Belf
MEDICAL UROLOGIST, DEPARTMENT OF MEDICINE, THE QUEEN'S UNIVERSITY OF BELFAST, AND BELFAST CITY HOSPITAL

C M B FIELD
M D Belf , M R C P E , D C H
PÆDIATRICIAN, BELFAST CITY HOSPITAL

HYPERPARATHYROIDISM may present itself in many clinical guises This case is recorded because of the unusual sequence of events which led to the diagnosis A baby was admitted to hospital with tetany, and because of this the mother's serum-calcium was estimated She was free from symptoms but was found to have hypercalcæmia Eventually, a parathyroid adenoma was removed Hyperparathyroidism in the mother has been diagnosed before because of tetany in the baby (Friderichsen 1939, Bruce and Strong 1955) but the previous patients differ from ours in showing obvious clinical signs of hyperparathyroidism

Methods

Serum-calcium was determined by the standard method, using oxalate precipitation and titration with permanganate Each sample of the mother's blood was determined in duplicate

Phosphorus was determined by the method of Fiske and Subbarow (1925), and creatinine by a modification of the method of Peters (1942) Mannitol infusion was carried out as described by Fourman et al (1960) Calcium infusion of 15 mg per kg was done over a four-hour period from 10 A M to 2 P M after four days of a low-calcium diet Four-hourly urine collections were made for twenty-four hours before infusion (control) and for twenty-four hours afterwards

Case-record

The baby—A full-term boy, weighing 9 lb 10 oz , was delivered normally, and progressed satisfactorily on artificial feeding until the fourth day of life, when twitching of the face and limbs began This gradually increased until, by the sixth day, it had become continuous, and he was admitted to hospital Apart from these movements, no other abnormalities could be discovered on clinical examination He fed well, and had a normal cry Chvostek's and Trousseau's signs were negative No albumin or reducing substances were present in the urine, the cerebrospinal fluid was normal, the blood-urea was 43 mg per 100 ml , and the serum-calcium 5 9 mg , X-rays of the skull and hands were normal 10 ml of calcium gluconate was given intravenously, and this relieved the movements for five hours Intermittent therapy with intravenous calcium gluconate was given whenever twitching occurred or the serum-calcium fell After the fourteenth day, effervescent tablets of calcium glucono-galacto-gluconate (Sandoz) were given by mouth, the dose varying from three to five tablets daily After thirty-three days the dosage was reduced, and was finally stopped when the infant was three months old During the entire time, the infant fed well, gained weight, and appeared bright and alert Serum-calcium, serum phosphorus, and alkaline-phosphatase values are given in table I

TABLE I—BLOOD-CHEMISTRY OF INFANT

Age (days)	Serum calcium (mg per 100 ml)	Serum phosphorus (mg per 100 ml)	Alkaline phosphatase (King Armstrong units)
6	5 9		
8	7 2		
12	5 8		
16	6 5	4 4	22
18	7 8		
25	8 1	10 3	51
27	8 5	10 0	25
33	10 0	7 9	30
39	11 0	8 5	29
49	10 0	4 3	6

The mother—A multipara, aged 28, was completely free from symptoms, and had never suffered from symptoms referable to the urinary tract or to the skeleton She was energetic and had an excellent appetite She did not suffer from any form of dyspepsia, and was not constipated During the recent pregnancy, she had severe nausea and vomiting from the fourth to the twentieth week, although during her previous three pregnancies she had had only slight morning nausea from the fourth to the twelfth week At the thirty-sixth week she was severely anæmic and the hæmoglobin rapidly fell to 42% (6 1 g per 100 ml) The red cell count was 2 7 million per c mm at this time The blood-film was said to show a normocytic, hypochromic anæmia, but later megaloblasts were found in the " buffy " layer Bone-marrow showed megaloblastic erythropoiesis The anæmia was treated with transfusions of packed cells, 'Fersivenin', and folic acid During the last four weeks of the pregnancy she again had severe vomiting

Three weeks after delivery, she appeared perfectly healthy She was not anæmic, and there was no abnormality in the skeletal system The kidneys were palpable, but not tender The only abnormality was that the blood-pressure was raised—160/95 mm Hg

TABLE II—BLOOD-CHEMISTRY OF MOTHER

Date	Serum calcium (mg per 100 ml)	Serum phosphorus (mg per 100 ml)	Urine calcium (mg per 24 hours)
Nov 2, 1959	10 7	2 5	
Nov 16	12 1	2 7	
Nov 23			18 (normal diet)
Feb 12 1960	12 2	3 4	
April 13	14 6	2 5	
April 17			63 (low calcium diet)
April 19	11 5	3 0	
April 24*	10 0	3 9	
June 10*	10 5	3 1	

* After operation

X-rays of the urinary tracts did not show any calcification, and there was no abnormality in X-rays of skull and hands Hæmoglobin was 15 9 g per 100 ml , hæmatocrit value was 48%, and the mean corpuscular hæmoglobin concentration was 33% On her first visit, the serum-calcium was 10 8 mg per 100 ml but the serum-phosphorus was 2 5 mg per 100 ml On all subsequent occasions the serum-calcium was raised (table II) The serum-proteins were 6 2 g per 100 ml with a normal electrophoretic pattern The alkaline phosphatase was 11 5 King-Armstrong units Three weeks after delivery, the urinary excretion of calcium was low on a normal diet and it was also in the low normal range five months later on low-calcium intake (150 mg per twenty-four hours) The blood-urea was 38 mg per 100 ml and the glomerular filtration-rate was 70 ml per min (clearance of endogenous creatinine) The ratio of the clearances of phosphate and creatinine, after four days on the low-calcium diet and in the fasting state, was 0 05 at a serum-phosphorus level of 3 0 mg per 100 ml This is within the normal range (McGeown 1957), and the phosphate-excretion index (Nordin and Fraser 1960) was – 0 046—also within the normal range The response to intravenous infusion of calcium was also normal, the serum-phosphorus rising to 1 1 mg per 100 ml and there being a fall (82%) in urinary excretion of phosphate compared with the control day The urine osmolality under conditions of dehydration rose to 1075 milliosmoles per litre, and in response to mannitol infusion it fell to 610 milliosmoles per litre (normal) After loading with ammonium chloride (0 1 g per kg), the urine-pH fell to 5 3

At operation, the left upper parathyroid gland was large and reddish It was removed, and was found to measure 1 8 1 1 0 3 cm The right and left lower parathyroids both appeared to be normal, but the right upper one could not be identified despite a careful search Histologically, the left upper parathyroid was an adenoma, largely composed of chief cells, with a tendency to form acini

Convalescence was uneventful Four days after parathyroidectomy, the serum-calcium was 10 0 mg per 100 ml and the serum-phosphorus was 3 9 mg The blood-pressure was 153/80 mm Hg

Discussion

There are several features of interest in this case The hyperparathyroidism was diagnosed before there were either renal calculi or detectable bone changes The previously reported patients both had bone changes and renal calculi In Friderichsen's (1939) patient, as in ours, the finding of tetany in the infant led to investigation of the mother The child reported by Bruce and Strong (1955) showed symptoms at the age of 1 year, and the diagnosis of hyperparathyroidism was made at 3$^1/_2$ When the child was 6, hyperparathyroidism was recognised in the mother Both the previously reported infants were breast-fed and did not develop tetany until some time after weaning Our infant was bottle-fed from birth, and tetany was apparent on the fourth day

The patient's feeling of wellbeing despite a considerable elevation of the serum-calcium level was an unusual feature The nausea and vomiting during the last pregnancy was probably due to the hypercalcæmia, as she had experienced only slight morning nausea during her previous three pregnancies, and it is our impression that women usually follow the same pattern of gastrointestinal symptoms in successive pregnancies The baby's alkaline phosphatase was somewhat high even for the neonatal period, which suggests that its skeleton had been subjected to the action of the mother's excessive circulating parathyroid hormone A pregnancy two years earlier had been completely normal, without vomiting or anæmia, this is presumptive evidence that hyperparathyroidism had not been present then The relatively brief duration of the hyperparathyroidism probably explains the absence of both renal calculi and bone changes

The level of the mother's serum-calcium was normal when she was first seen, although it was afterwards always elevated Many patients with hyperparathyroidism have a normal serum-calcium from time to time, interspersed with elevated values (McGeown and Morrison 1959) One normal value for the serum-calcium is never sufficient to exclude hyperparathyroidism if there are clinical grounds for suspecting it The serum-phosphorus also usually fluctuates, as it did in this patient The urinary calcium was not elevated on either of the occasions when it was estimated, although there was only minor impairment of renal function

Since various measures of urinary phosphate excretion are widely used to assess parathyroid function, it is interesting that the ratio of the clearances of phosphate and creatinine was normal for the level of the serum-phosphorus, as was the phosphate-excretion index (Nordin and Fraser 1960) The response to intravenous infusion of calcium also followed the normal pattern Fourman et al (1960) have suggested that tests of renal tubular function may have diagnostic value in hyperparathyroidism, but this patient behaved normally during osmotic diuresis induced by mannitol infusion, and in response to ammonium-chloride loading, as have other patients we have studied (McGeown 1960) In fact, the more specialised tests of parathyroid function were all without value in diagnosis in this patient This has often been our experience amongst patients suffering from relatively mild hyperparathyroidism of short duration

We wish to thank Mr Ernest Morrison, F R C S E , who carried out the parathyroidectomy

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INFLUENCE OF OXYGENATION AND DEOXYGENATION ON DISTRIBUTION OF INSULIN ACTIVITY AMONG BLOOD-PLASMA-PROTEIN FRACTIONS

D C GARDINER
ASSISTANT, DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CAMBRIDGE
D MARTIN-HERNANDEZ *
D Sc Madrid
F G YOUNG
M.A Cantab , D Sc Lond , F R S
PROFESSOR OF BIOCHEMISTRY, UNIVERSITY OF CAMBRIDGE

THE insulin activity of the blood in the venous drainage to the pancreas, measured biologically (rat-diaphragm method or rat-adipose-tissue method), is less than that in simultaneously sampled arterial blood, and oxygenation of blood, either in the lungs or in vitro, can lead to a rise in the biologically estimated insulin activity (Young 1959, 1961) The present investigation was made to determine the distribution of insulin activity among fractions of plasma-proteins prepared from arterial and venous bloods, obtained from animals, or from blood oxygenated or deoxygenated in vitro

Methods

Estimation of Insulin Activity

The method of Randle (1956), involving the use of isolated rat diaphragm suspended in the buffer described by Gey and Gey (1936), was used

In its application to blood-serum or blood-plasma, 0 5 ml and 0 1 ml samples of the serum or plasma were diluted to 2 0 ml with buffer for the estimation of glucose uptake by one hemidiaphragm Otherwise samples—usually 2 mg —of freeze-dried fractions from plasma-protein fractions were dissolved in 2 ml of buffer, and the influence on the glucose uptake of isolated rat hemidiaphragms was determined in the usual way

Blood

In some instances samples of arterial and venous blood were withdrawn almost simultaneously from anæsthetised (pentobarbitone) animals through polyethylene catheters into centrifuge pots containing paraffin oil In experiments in which the plasma was to be fractionated, the centrifuge pots also contained citrate as an anticoagulant, but no anticoagulant was used where estimations were to be carried out on unfractionated serum

In other instances blood was obtained from the slaughterhouse, either defibrinated or treated with citrate as an anticoagulant Samples of the same lot of blood were oxygenated or deoxygenated in vitro by bubbling through them a mixture of 95% oxygen with 5% carbon dioxide, or 95% nitrogen with 5% carbon dioxide, as described by Young (1961)

Fractionation of Blood-plasma

Fresh citrated plasma, or, in a few instances, defibrinated serum, was fractionated by the method of Lever et al (1951), which involves separation by precipitation with ethanol at

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* Juan March Foundation Fellow (Spain) in the Department of Biochemistry University of Cambridge.

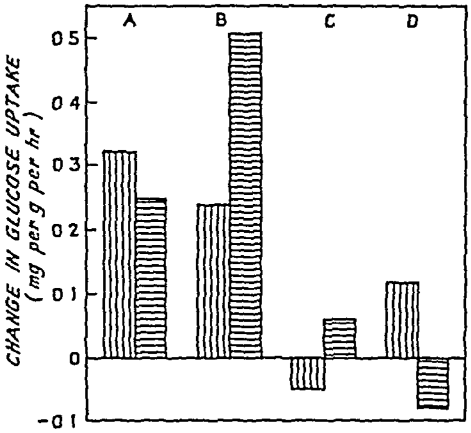

Fig 1—Activity in rat-diaphragm test of protein fractions prepared from serum from deoxygenated pig blood (vertically hatched columns) and oxygenated pig blood (horizontally hatched columns) by the method of Lever et al (1951)

Fraction A=fractions I+III of Lever et al
Fraction B=fraction II (γ-globulins) of Lever et al
Fraction C=fractions IV+V (albumins &c) of Lever et al
Fraction D=fraction VI of Lever et al

An average of 1 mg per ml of buffer/hemidiaphragm of each fraction was used in the tests, and the columns represent mean values for 16–24 rats

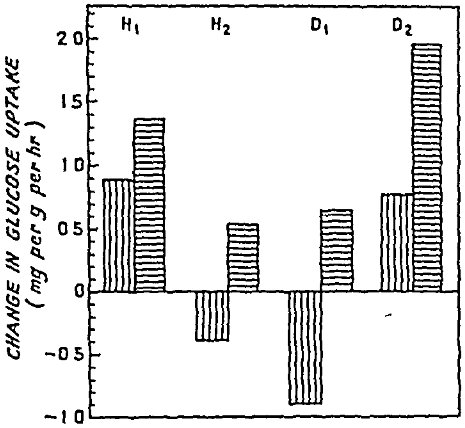

Fig 2—Activity in rat-diaphragm test of γ-globulins prepared from deoxygenated or venous blood (vertically hatched columns), and from oxygenated or arterial blood (horizontally hatched columns)

H_1=human blood Sample 1
H_2=human blood Sample 2
D_1=dog blood Sample 1
D_2=dog blood Sample 2

1 mg per ml of buffer/hemidiaphragm of each fraction was used, and the columns represent the mean values for 4–8 rats

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−5°C under controlled conditions Dialysed solutions of the separated fractions were freeze-dried and stored at low temperature for subsequent insulin assay Four main fractions are obtained in this way—designated fractions A, B, C, and D for the purposes of the present investigation According to Lever et al (1951), the fraction we designate A (=their fractions I+III) contains β_1-lipoproteins, β_1-lipid-poor euglobulins, and other globulin-like proteins Our fraction B (=their fraction II) consists of γ-globulins, our fraction C (=their fractions IV+V) contains serum-albumins, and some α_2-glycoproteins and α_1-lipoproteins, while our fraction D (=their fraction VI) contains traces of albumins and of small proteins in general

In our hands, fraction A amounts to about 15% of the total material recovered after fractionation Similar amounts of fraction B (γ-globulins) are obtained, while the fraction C (largely serum-albumins) amounts to about 60% of the total recovered We find that fraction D varies in amount, but averages about 10% of the total recovered

Results

Fig 1 shows the mean results for all four fractions from oxygenated and deoxygenated pig blood-plasma

The γ-globulins (fraction B) from the oxygenated blood contain more than twice as much insulin activity as those from deoxygenated blood, the difference being highly significant ($P < 0.01$) A smaller difference is also seen with the albumin fraction (fraction C), though this difference is not statistically significant on the basis of the number of experiments done Differences in the opposite direction, though not significant statistically, are seen with fractions A and D

With blood from other species examined (human, dog, rabbit) the general pattern of differences between the fractions from oxygenated and deoxygenated bloods is similar, although variations are seen from one individual blood sample to another

Fig 2 shows the results found with individual samples of the γ-globulins (fraction B) of blood from human beings and from dogs Though differences occur between the absolute results for the different samples, the γ-globulins from oxygenated blood all contain more insulin activity than those from deoxygenated blood In every instance the difference was statistically significant ($P < 0.05$) With one sample of human blood and one of dog blood, the γ-globulins from the deoxygenated sample exerted, not an insulin-like action, but an action which depressed the glucose uptake of the isolated rat diaphragm—that is, it possessed an insulin-inhibitory action

As is shown in fig 1, the albumin fraction (fraction C) from deoxygenated pig blood also exerted an insulin-inhibitory action, as opposed to the insulin-like activity of the albumin fraction from arterial blood Although this difference is not statistically significant on the basis of the number of experiments we have carried out, an inhibitory action of albumin from deoxygenated or venous blood of the species we have examined has been consistently found in our experiments This may be of physiological importance, despite the smallness of the effect seen, because of the magnitude of the albumin fraction

The curious result with fraction D (fig 1) is also repeatable with the samples of plasma we have examined so far, the effect is small, and the amount of fraction D variable, and we have insufficient data yet to assess the possible significance of these findings

In preliminary results with dog (greyhound) blood obtained from the anæsthetised animal we have, with samples from four different animals, obtained a reversed dose-response curve with unfractionated serum from both oxygenated and deoxygenated blood That is to say, the effect of 0.5 ml of serum (diluted to 2 ml with buffer) on the glucose uptake of isolated rat diaphragm is less than that of 0.1 ml (diluted with buffer to 2 ml) Such an effect may be related to the action of insulin antagonists of the type described by Vallance-Owen (1960) Whether this observation is peculiar to the greyhound is a matter for further investigation, but it is true that, despite the anomalous dose-response relationship for the unfractionated serum, the difference between venous and arterial blood serum described by Young (1961) is still seen

Discussion

The results obtained with the fractions of plasma-proteins agree with the observation of Young (1959, 1961) that an important change occurs in the insulin-like activity of serum or plasma when blood passes through the lungs or is otherwise oxygenated, the process being largely reversed when the blood becomes deoxygenated by passage through the tissues or otherwise The observations with plasma-protein fractions so far recorded suggest that the most important change occurs in the γ-globulin fraction (fraction B) and is such that oxygenation of the blood greatly increases the insulin-activity of the γ-globulins, in some instances converting a significant inhibitory action on isolated diaphragm to a substantial insulin-like activity Quantitatively, the changes in the γ-globulin fraction probably contribute most to the total result seen with diluted whole serum or plasma (cf Young 1961), but the contribution of the other fractions cannot be ignored As yet no attempt has been made to compare the integrated activities of the various fractions with that of the whole plasma, but with the reversal of the normal dose-response relationship seen with blood-serum of the greyhounds, examined under the conditions described by Randle (1956) for the assay of plasma-insulin activity, the dose-response relationships for the separated fractions merit more investigation than has so far been possible In general, preliminary investigations suggest that the differences between the activities of γ-globulin fractions from oxygenated and deoxygenated bloods do not greatly vary with the amount of the fraction tested, provided that a dose is tested which is large enough to have a significant effect on isolated diaphragm

Most of the experiments described here have been carried out with blood oxygenated or deoxygenated in vitro, but similar results were seen with blood obtained in a naturally arterial or venous state For example, experiment D_2 (fig 2) was one carried out with naturally arterial and venous bloods

Young (1961) was cautious in ascribing the results with serum or plasma to the action of insulin itself, but the present experiments have largely been carried out with 2 mg of the fractionated plasma-proteins dissolved in 2 ml of buffer—conditions in which the non-specific effects of plasma-proteins are likely to be very slight Young (1961) recorded negative results for experiments designed to reveal an enhancement or diminution of activity of insulin added to blood which is then oxygenated or deoxygenated in vitro Such negative results, combined with the observation of the substantial inhibitory activity in the diaphragm test of some γ-globulin fractions from deoxygenated blood, suggest that the oxygenation and deoxygenation of the blood may be exerted on the activity of insulin inhibitors or antagonists rather than on insulin itself, though no final conclusion about this can yet be drawn The distribution of such inhibitors or antagonists among the plasma-proteins may also be influenced

As recorded by Young (1961), oxygenation and deoxygenation of separated plasma or serum under conditions similar to those used for whole blood exert no significant effect on the insulin activity of the plasma or serum, and the effect of oxygenation appears to depend on the presence of the cellular components of the blood, most probably the erythrocytes

The possible physiological implication of these results was discussed by Young (1961), and, although the present findings do not extend the scope of such considerations, they do reinforce them From a practical point of view it seems unwise to regard venous blood as similar to arterial blood for the purposes of any biological (or, indeed, non-biological) assay of blood constituents until evidence is available that such an assumption is justified The possible role of the lungs in altering the biological activity of constituents of the blood-plasma clearly merits further research With respect to the assay of insulin activity in blood-plasma by biological means, the differences in results for whole plasma between different laboratories, and the similar differences in the results for separated fractions of plasma-proteins (Randle and Taylor 1960) might well be influenced by whether or not samples of venous blood have become oxygenated during the preparation of plasma or serum Again, further investigation is needed to throw light on this question

Summary

The observation of Young (1961) that plasma or serum from arterial blood, or from blood oxygenated in vitro, exerts a greater insulin-like activity on isolated rat diaphragm than does plasma or serum from comparable venous blood, or blood deoxygenated in vitro, has been extended by an examination of the insulin activity of separated plasma-protein fraction

In the γ-globulin fraction from arterial or oxygenated blood, prepared by the method of Lever et al (1951), significantly greater insulin activity was found than in a similar fraction from comparable venous or deoxygenated blood

The albumin fraction prepared by the method of Lever et al (1951) showed qualitatively similar, but not statistically significant, differences Differences between other fractions were also observed, but these also were not statistically significant on the basis of the number of experiments performed

The increase in insulin activity of the blood-plasma which results from oxygenation of the blood is therefore associated with an alteration in the distribution of insulin activity among plasma-protein fractions In particular, the insulin activity of the γ-globulin fraction is raised The possibility is discussed that oxygenation of the blood causes a reversible depression in the activity of insulin inhibitors or antagonists present in plasma proteins, as well as a possible redistribution of them among the protein fractions Other mechanisms clearly may play a part Such a postulated depression in activity of insulin inhibitors or antagonists would be reversed when blood passes naturally from the arterial to the venous state, or is deoxygenated in vitro

Possibly the lungs not only oxygenate the blood passing through them but also alter the biological activity of some of the constituents of the blood-plasma, of which insulin is one

We thank the British Diabetic Association for a grant for expenses which made this research possible We are indebted to Dr R S Comline, department of physiology, University of Cambridge, for obtaining blood samples from animals under carefully controlled conditions on our behalf

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NATURAL RADIOACTIVITY IN WEST DEVON WATER-SUPPLIES

JOHN D ABBATT
M B Edin , D M R
MEDICAL RADIOBIOLOGIST AND CHIEF MEDICAL OFFICER,
GENERAL ELECTRIC COMPANY LTD , ERITH, KENT

J R A LAKEY *
B Sc , Ph D Sheffield, A Inst P

D J MATHIAS
SENIOR HEALTH PHYSICISTS, MEDICAL RADIOBIOLOGY DEPARTMENT,
ATOMIC ENERGY DIVISION, GENERAL ELECTRIC CO , LTD , ERITH, KENT

A RECENT report on the uneven distribution of cancer in West Devon (Allen-Price 1960) suggests that some agent or agents associated with the water-supplies was responsible for the uneven distribution The incidence of cancer (deaths per 1000 living) was shown to vary between areas with different sources of drinking-water Though the evidence was not conclusive, it was clear that an investigation of the water-supplies would be of great interest, and their radioactivity is now being investigated

Radioactivity is not necessarily the only factor, and only some of the preliminary results are given here, since they are of sufficient interest and importance to be described separately

The objects were to determine whether any of the water-supplies contained measurable quantities of radioactive material, to identify the source and nature of any activity, and, if possible, to make a quantitative assessment

Water Sampling

Collection

Samples from West Devon sources collected in 5 6-litre polyethylene jars—a method chosen for convenience of collection and transport but in the light of subsequent measurements perhaps not the best method The first step was a crude measurement of any radioactive material in the water, preferably without chemical treatment of the samples so that later chemical analysis would not be prejudiced Before they were used, all the sample bottles were made chemically clean, rinsed in distilled water, and tested for radioactivity

Samples were taken from drinking-water taps, wells, reservoirs, and surface supplies, such as quarry chutes Most sources investigated have recently been replaced by mains water for human drinking, so an accurate correspondence between the water sampled and cancer incidence in the area it supplied is not yet possible The past histories of the water-supplies and the people supplied are being investigated

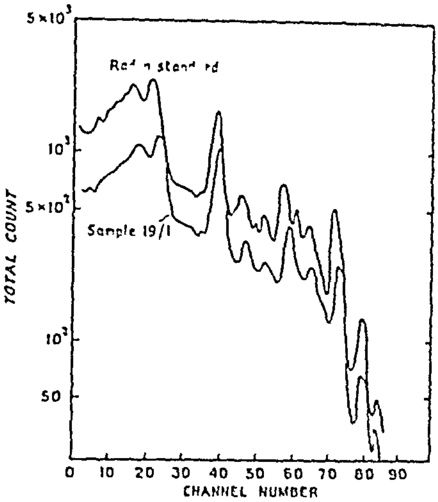

Fig 1—Identification of radon in Devon water Gamma spectrum of Devon water sample compared with the spectrum of known radon standard There is some drift in position of peaks due to the necessary long counting times (see appendix)

Counting

In the radioactive counting laboratory at Erith, environmental radioactivity is measured in preparation for the commissioning and operation of nuclear power stations For the initial radioassay of the water samples the existing techniques of the laboratory were used, but more sophisticated methods are being developed

The samples came from Devon by train, and the routine counting method was then applied

(1) Exterior of the sample bottle washed with inactive water
(2) Background count carried out on a large heavily shielded sodium iodide crystal using distilled water
(3) Apparatus calibration count with radon water or a radium solution
(4) Sample count with date and time recorded
(5) Daily repeat counts where possible (for half life determination, &c)

Further details are given in the appendix

Results

The estimated specific activities at the time of collection of 51 samples and their source (well, tap, reservoir, chute, &c) are given in the table All samples came from drinking-water sources (some now disused or closed) referred to by Allen-Price (1960)

RADIOASSAY OF WATER SAMPLES

Code no	Source (tap well reservoir chute &c) and date (1960)	Specific activity estimated at time of collection (μμC per ml radon + daughters)	Code no	Source (tap well reservoir chute, &c) and date (1960)	Specific activity estimated at time of collection (μμC per ml radon daughters)
1 1	Town supply (tap) March 9	0 1	13 3	Reservoir Sept 21	8 3
2 1	Spring (reservoir) May 12	1 3	13 4	Tap May 10	8 5
2 2	Reservoir April 6	<0 1	13 5	Tap (well) ,, 10	7 4
2 3	Well (tap) May 12	0 8	15 1	Reservoir Sept 28	2 0
2 4	Well March 10	5 0	15 4	Pump Oct 19	0 2
2 5	Well 10	2 1	15 5	Pump May 10	1 9
2 6	Spring May 12	0 1	17 1	Chute Oct 17	0 6
2 7	Well ,, 10	2 1	17 2	Chute May 11	0 1
3 1	Well 11	<0 1	17 3	Well 11	1 9
4 1	Chute April 6	5 [illegible]	18 1	Reservoir Sept 28	2 0
4 1	Chute May 4	9 8	18 2	Spring May 10	<0 1
4 2	Spring April 6	2 0	19 1	Reservoir March 9	[illegible] 0
4 2	Spring May 4	1 6	19 2	Well (pump) May 5	[illegible] 1
4 4	Pump May 4	1 2	19 3	Well ( ) 5	13 3
4 5	Spring Oct 19	0 3	19 4	Well ( ) 5	5 4
5 4	Spring March 10	2 3	21 1	Pump 11	[illegible] 3
6 1	Spring Oct 26	0 3	21 2	Pump 11	1 9
8 1	Reservoir April 5	8 6	21 3	Pump 3	1 1
8 1	Reservoir May 5	5 4	22 1	Well Oct 17	0 1
8 2	Spring Sept 21	0 9	22 2	Pump May 3	2 2
8 3	Mains water (tap) 21	0 1	22 3	Spring (tap) Sept 2[illegible]	0 1
9 1	Tap (well tank) Oct 24	3 0	23 1	Reservoir (tap) 26	0 2
10 1	Pump May 4	0 1	23 2	Spring (tap) May 3	1 2
10 2	Pump 3	1 4	25 1	Tap Sept 21	4 0
11 1	Tap (spring) Oct 24	0 5	2[illegible] 1	Chute March 5	[illegible] 1
12 2	Reservoir May 11	0 1			

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* Present address Department of Nuclear Science and Technology, Royal Naval College Greenwich London, S E 10

Fig 1 shows a gamma spectrum of a typical high-activity water sample, and compared with the spectrum of a known radon sample The results of gamma spectrometry and half-life determinations (see appendix) identified radon as being at least primarily responsible for the gamma activity of the samples

Discussion

These assays of water from West Devon show that natural radioactivity varies from less than 0 1 $\mu\mu$C per ml to 13 3 $\mu\mu$C per ml The same variation in natural radioactivity has been noted in other parts of the United Kingdom It is still too early to speculate on the exact relationship between the incidence of cancer and the radioactivity of drinking-water, but the variations in activity of water reported here are similar to, or greater than, the variations in the natural activity of foods recently recorded by Turner, Radley, and Mayneord (1958)

As a precautionary measure all the appreciably radioactive water-supplies in West Devon have been cut off and replaced by inactive supplies

Though it is now clear that some waters are highly radioactive in this area where unexpected variations in cancer incidence have already been demonstrated, there is not yet enough material to allow a satisfactory statistical analysis An intensive integrated programme of measurements (both of radioactivity and trace elements) is therefore being conducted, together with a social survey The principal aim is to determine the extent of individual and hence of population exposure The whole investigation, of which this report is only a facet, is being coordinated by Prof J S Mitchell, regius professor of physic in the University of Cambridge

Summary

Wide variations in the natural radioactive content of water-supplies have been demonstrated in West Devon and elsewhere Unexpected variations in cancer incidence, apparently related to water-supplies, have also been reported in West Devon

An intensive programme of measurement of radioactivity and a social survey is now being conducted in West Devon to try to define the extent of individual exposure in the area to radiation and to any other agents in the water, and to relate this exposure to any effects that may be produced

We should like to thank Dr E D Allen-Price and Miss P B Fletcher for their invaluable advice and assistance, particularly with water-sampling We are particularly grateful to Professor Mitchell for his continued advice, support, and criticism The social survey is being carried out with the generous support of the Joseph Rowntree Memorial Trust Our thanks are also due to L P Gorman for technical assistance, and to the General Electric Co Ltd for permission to publish measurements made in the laboratory of the medical radiobiology department at Erith, Kent

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Appendix

MEASUREMENT OF RADIOACTIVITY

Assay of Total Activity, Spectrum Analysis, and Half-life Determinations

Water samples were collected in 5 6 litre polyethylene bottles, taking care not to disturb the water, and samples were usually free from sediment and debris The screw caps were sealed tightly, and marked with a code number and time and date of collection They were despatched by overnight train, and most of them were received at Erith for counting 12 hours later The outsides of the bottles were then washed, rinsed with distilled water, and counted on a gamma scintillation counter

The apparatus consisted of a 3 in deep × 3 in diameter sodium iodide phosphor or crystal encapsulated in aluminium with a glass window (Nuclear Enterprises [G B]) and optically coupled to a 5-in diameter type EMI 6099 photomultiplier tube (E M I Electronics) This assembly was light-tight and was mounted inside a cylindrical steel shield, approximately 5 in thick with an internal diameter of 8 in The crystal was protected with a clean sheet of paper and the water sample in the 5 6-litre bottle was placed on top of the phosphor The photomultiplier was coupled to it by way of a cathode follower to a type NE 5202 non-overloading wide-band amplifier (Nuclear Enterprises) and E H T was obtained from a type-532 stabilised power unit (Isotope Developments) The output pulses were counted on a type-1009E scaler (Dynatron Radio) Pulse-height analysis was carried out on a Marshall 100-channel pulse-height analyser (Marshall Cambridge), or on a type-N101 single-channel pulse-height analyser (Dynatron Radio)

For the initial tests the apparatus was calibrated with a solution of ^{131}I in the 5 6-litre bottles The iodine gamma-rays were counted at an efficiency of about 3% against a background of about 500 counts per minute Many of the water samples tested had high enough activities to produce identifiable gamma spectra, and one of these is shown in fig 1

The channel width of the spectrometer increases exponentially with channel number The energies of the peaks were checked against ^{13} Cs and ^{60}Co standards, and comparison with published spectra suggested that the activity was due to radon and its daughter products Subsequent tests with water containing radon confirmed that this element was the principal source of the observed gamma activity, and a radon spectrum is superimposed in fig 1 to illustrate the agreement The duration of the sample count was about 20 minutes, so some drift is apparent in the position of the peaks

To confirm the presence of radon, 1 mC samples of radon gas in glass seeds were obtained from the Radiochemical Centre, Amersham The glass seeds were broken inside a 20 ml metal and glass syringe which was connected to a standard blood-transfusion bottle by puncturing the rubber seal with the syringe In this way most of the radon gas was transferred to the bottle, and after a suitable delay for equilibrium to be established, aliquots were removed with a second syringe to be diluted in the 5 6-litre bottles These samples were used for the qualitative comparison described above

An accurate calibration with these samples proved difficult due to (*a*) the adsorption and absorption, &c , of radon and its daughter products on the walls of the vessel, and (*b*) the possibility that some of the radon sample was not transferred or not uniformly mixed in the standard bottle

The geometry of the counting system was tested by (*a*) diluting a 1-litre sample in a 5 6-litre bottle in steps of 1 litre and counting at each step until the bottle was filled, and (*b*) removing water from a full bottle, again counting at each step

After correcting for the continued reduction in specific activity it was found that the count did not increase significantly with more than $4^{1}/$ litres in the bottle In all cases the emptied bottle showed a significant count due to residual activity on the vessel wall For the preliminary tests this effect was neglected since in all cases the bottles were counted full Using the solutions made up from Amersham radon samples, a sensitivity of 320 c p m above background for each 1 $\mu\mu$C of radon plus daughters per ml was obtained

To check this and also to provide a convenient standard for subsequent counting (i e , one which would not decay significantly) a sample of radium (0 068 μC±20%) in association with 100 mg barium chloride (A R C C source type RC34) was dissolved in distilled water and made up to a full 5 6-litre bottle This gave 340 c p.m above background for 1 $\mu\mu$C of radium in association with its short-lived daughter products (radon, radium A, radium B, radium C) which have, of course, essentially the same gamma spectrum as radon plus daughters This calibration figure was not used, but all counts were referred to the radium sample to correct for variations in the apparatus As a further check a radon seed (sealed) was inserted into a 5 6-litre bottle filled with distilled water at various points above the base, and a weighted mean value of the sensitivity obtained was found to be equivalent to 290 c p m per 1 $\mu\mu$C per ml , a reasonable agreement

Where possible, counting was repeated on three consecutive days, and the sample activity was deduced from the extrapolated count-rate expected at the time of collection of the sample The radioactive decay of some samples was observed over 14 days and apparent half-lives of between 3 0 and 3 3 days were observed These values are well below the true radon half-life of 3 825 days, but are within the limits of accuracy of these preliminary measurements

Other Tests

To ascertain whether radon gas was responsible for the activity some samples were subjected to a variety of tests

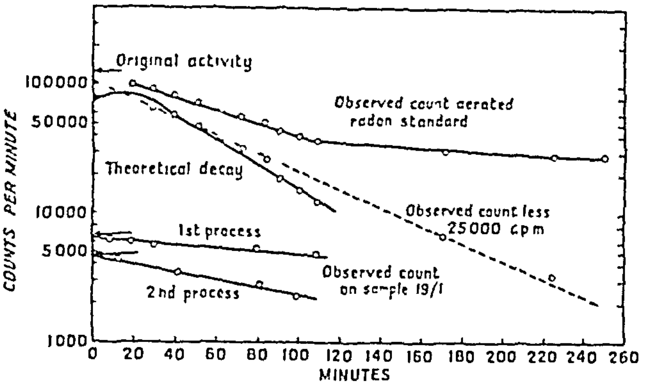

Fig 2—Effect of bubbling (aeration) on radon standard in distilled water and on Devon water sample Bubbling reduces gamma activity of radon water and to a lesser extent that of Devon sample The process was repeated in Devon sample where impurities and particulate matter were present

Some samples were treated with a mixed-bed ion-exchange resin (Bio demineralite, Permutit Co) Both the resin and the effluent were then counted The activity of the resin decayed with approximately the theoretical half life of radon daughter products and the effluent increased in gamma activity, reaching equilibrium at a lower value than that before treatment after about 2 to 3 hours

Some samples were treated by boiling, or by bubbling air through the open sample, and in each case showed a reduction in gamma activity (fig 2)

A simplified method, which was later used on site was filtration of the water through a millipore filter (A F 600 membrane filters, Membranfilter-Gessellschaft) and the beta activity of these discs was counted with the aid of a GM2 Geiger-Mueller end window beta-counter This method removed the daughter products from the water samples with variable efficiency, but in all cases the daughters could be identified by half life The beta activity of the daughters could be detected with an efficiency of about 30% so that this method, although not reliable for quantitative work, gave an easy field method of detecting the more active sources

The quantitative results obtained by this method confirm that radon gas is the main source of activity, but do not exclude the possiblity of the presence of small quantities of longer-lived activity

EFFECT OF TRIIODOTHYRONINE ON SERUM-BILIRUBIN LEVEL AND NEONATAL DEVELOPMENT OF THE PREMATURE INFANT

H SHRAND
M B Cape Town, M R C P , D C H
LATE RESIDENT PÆDIATRIC OFFICER*

C R J RUTHVEN
M Sc Lond , F R I C
BIOCHEMIST

QUEEN CHARLOTTE'S MATERNITY HOSPITAL, LONDON, W 6

IN a controlled trial of triiodothyronine in neonatal hyperbilirubinæmia, Lees and Ruthven (1959) found evidence of some lowering of the serum-bilirubin levels in treated infants As these effects were more apparent in premature babies, we have carried out a further trial, confined to this group, but using double the previous dose of the drug

Methods and Results

For the first five days of life, premature infants between 900 and 2100 g birthweight were allocated at random to a treatment group or to a control group The treated infants received 10 μg triiodothyronine ('Tertroxin', 3 5 3'-triiodo-L-thyronine sodium) in a single daily dose mixed with a little of the feed Serum-bilirubin was determined by methods of Lees and Ruthven (1959) on the first day of life, and then daily until the peak level was passed Weight, temperature, feeding ability, and general state of alertness or lethargy were noted daily Infants with Rh and ABO incompatibility were excluded from the trial

The mean peak bilirubin-level in the treated series was higher than in the controls (table I), but this difference was not significant at the 5% level (t = 1 86, 0 05 < P < 0 1) The mean period between the day of birth and the day of peak bilirubinæmia level, although longer in treated babies, did not differ significantly from the mean time taken by the control group (table I)

The mean weight lost by the controls was less than the treated babies, although this difference was not statistically significant In both groups, the birthweight was regained within the same time (table II) No differences were observed between the control and treated infants in temperature regulation, feeding ability, degree of alertness or lethargy, or general appearance

TABLE I—TIME OF OCCURRENCE AND LEVEL OF THE BILIRUBIN PEAK

Group	No in group	Mean peak bilirubin level (mg per 100 ml)	Mean period from birth to reach peak bilirubin level (hr)
Control	14	8 95 ± 1 33	97 ± 10 9
Treated	14	11 5 ± 1 31	105 ± 11 6

Discussion

The findings of Lees and Ruthven (1959) that a daily dose of 5 μg triiodothyronine given to premature babies produced a decrease in mean bile-pigment level, suggested that the drug might accelerate bilirubin conjugation and consequently its excretion In this series, however, the prematures, although receiving double the previous dose of triiodothyronine, showed neither a reduction in bilirubin (table I) nor any improvement in their general development (table II)

Westphal et al (1959), who gave 25 μg triiodothyronine to newborn infants, found a statistically significant increase in the number of treated infants whose serum-bilirubin level either remained stationary or fell between the second and fourth day of life when compared with controls Because Westphal et al (1959) used different criteria from ours, and studied premature and full-term infants as one group, the two investigations are not strictly comparable

In all reported studies only small changes of mean bile-pigment level have been found, so it is conceivable that slight alterations in variables might account for the apparently contradictory results between the present trial and previous ones Although it is not possible from the evidence to pinpoint the difference, these factors might have played a part (1) a random selection instead of alternating trial and control infants, (2) the variation in the comparative mean birthweights of the test and

TABLE II—MEAN WEIGHT CHANGES DURING FIRST 14 DAYS OF LIFE

Group	No in group	Mean birth weight (g)	Mean weight loss (as percentage of birthweight)	Mean age at minimum weight (days)	Mean age at which birth weight was regained (days)
Control	14	[illegible]	6 8	4 0	13 0
Treated	14	1760	10 4	6 2	13 5

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* Present address: The Evelina Children's Hospital of Guy's, Southwark Bridge Road, London, S E 1

control groups in the respective trials, and (3) differences in weight-loss after birth. Birthweight influences the severity of neonatal jaundice (Billing et al. 1954), and weight-loss may be accompanied by hæmoconcentration which might result in a rise in bile pigment level (Lucey 1960).

As the triiodothyronine dosage used in this series lay between those given by Westphal et al. (1959) and Lees and Ruthven (1959) any connection between our increased dosage and the tendency to higher bilirubin levels in the test group can probably be discounted. Even so, some drugs given to the mother before delivery or to the newborn infant may increase the incidence of kernicterus, even in the presence of serum-bilirubin levels previously considered harmless (Harris et al. 1958, Lucey and Dolan 1959, Lucey 1960). Though there was no evidence in this trial that triiodothyronine had any such action, this possible danger, together with our present negative findings, suggests that there is no place for triiodothyronine in the treatment of neonatal jaundice.

Summary

During a randomly controlled trial of triiodothyronine in premature infants, it was not possible to confirm the previous claims that the drug lessened the degree of neonatal jaundice.

It is a pleasure to express our thanks to Dr. A. White Franklin, Dr. A. P. Norman, Dr. John Murray, Dr. Merton Sandler, and the research team at Queen Charlotte's Maternity Hospital.

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ANÆMIA DUE TO "BLUE-RUBBER-BLEB" NÆVUS DISEASE

G. M. BERLYNE
M.B. Manc., M.R.C.P.
TUTOR IN MEDICINE, UNIVERSITY DEPARTMENT OF MEDICINE,
MANCHESTER ROYAL INFIRMARY

N. BERLYNE
M.B. Manc., M.R.C.P.E., D.P.M.
ASSISTANT PSYCHIATRIST, ST. THOMAS'S HOSPITAL, STOCKPORT

> 'Disease is very old and nothing about it has changed. It is we who change as we learn to recognise what was formerly imperceptible.'
> —J. M. CHARCOT

CAVERNOUS hæmangiomas in the skin look and feel like blue-rubber blebs. Bean (1958) therefore called them "blue-rubber-bleb" nævi. Cavernous hæmangiomas in the bowel are well known for their tendency to bleed, producing either a chronic iron-deficiency type of anæmia or frank bleeding—hæmatemesis, melæna, or rectal bleeding. It is not generally realised that there is an association between cavernous hæmangiomas in the skin and those in the bowel, though several authors (McLure and Ellis 1930, Holman 1948, Heycock and Dickinson 1951, Rickham 1952, Shepherd 1953, Bean 1958) have stressed that in gastrointestinal bleeding of obscure cause, cavernous hæmangiomas in the skin suggest that similar lesions may be present in the bowel, and may be responsible for the blood-loss. This syndrome of cutaneous and intestinal cavernous hæmangiomas has generally escaped attention: it is little known and, consequently, rarely diagnosed. Its genetics have not been investigated hitherto, and only one author (Bean 1958) has presented a detailed family history.

We wish to draw attention to the existence of this disease, and to record for the first time its mode of inheritance as an autosomal dominant character in a family in which it can be traced through five generations.

Case-report

A small-holder, aged 52, complained of lassitude and dyspnœa on exertion. He said he had been anæmic for years owing to blood-loss from "piles" which had been bleeding at intervals of roughly four weeks since he was 17. The bleeding was worse on defæcation, but occasionally occurred at other times.

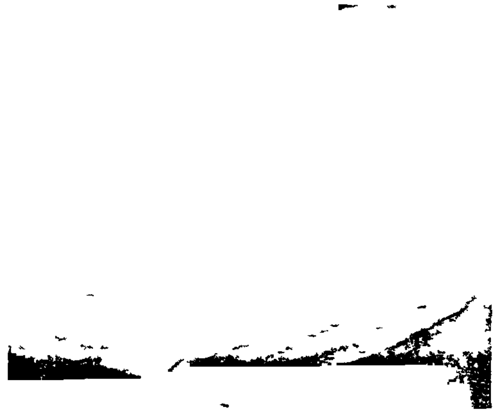

Fig. 1—Forearm of propositus showing several cutaneous cavernous hæmangiomas (blue-rubber-bleb nævi).

For many years he had suffered from intermittent rectal prolapse, although his "piles" never came down by themselves. He had had blue lumps in and under his skin for as long as he could remember. He thought they had become more numerous as he became older. They were painless, but a knock would cause a painful bruise at the site of the lesion. Whilst the patient was having psychiatric treatment for irritability in May, 1960, one of us (N. B.) noted the association of the skin lesions with a profound iron-deficiency anæmia.

In 1947, he had had a severe hæmatemesis, after which a gastroenterostomy was done for a suspected, but unconfirmed, gastric ulcer. The presence of the skin lesions was not recorded at the time, nor were any hæmangiomas noted in the bowel.

The patient was pale and looked chronically ill. His skin was covered with blue cavernous hæmangiomas, which felt like rubber blebs, being readily emptied of their contained blood by firm compression. Some were subcutanous, but most of them were intradermal, varying in size from 1 to 40 mm. No bruit was heard over them. The fingers were not involved, the lesions being scattered over the trunk, arms, and legs; there were a few on the face (fig. 1). The cardiovascular, respiratory, and central nervous systems were normal. The rectum would prolapse on straining, disclosing numerous cavernous hæmangiomas—some purple, some red—in the mucosa of the rectum; there were several bleeding points in the mucosa overlying the lesions. Proctoscopy, after replacement of the prolapsed rectum, showed the anal canal to be normal, though there were numerous cavernous hæmangiomas in the rectum. He had no bony deformities or oral lesions.

Investigations and Treatment

April 22, 1960: Hæmoglobin (Hb) 50% (7.4 g. per 100 ml.), red blood-cells (R.B.C.) 4.75 million per c.mm., colour index (C.I.) 0.52, white blood-count (W.B.C.) 6800 per c.mm. Oral iron was prescribed but the patient failed to take it, complaining of nausea which he attributed to the ferrous-gluconate tablets.

SERLOGICAL DIAGNOSIS IN LEPTOSPIRAL ASEPTIC MENINGITIS

CONSTANCE A C ROSS
M D Glasg
SENIOR REGISTRAR IN VIRUS DISEASES, RUCHILL HOSPITAL, GLASGOW

J C J IVES
M B Edin , F R F P S
TEACHER LECTURER IN BACTERIOLOGY, UNIVERSITY OF GLASGOW, AND CONSULTANT BACTERIOLOGIST, GLASGOW ROYAL INFIRMARY

MOST agents responsible for the syndrome of aseptic meningitis (" lymphocytic meningitis ") are viruses Indeed, the virus laboratory now receives far more specimens from cases of aseptic meningitis than does the bacteriological laboratory Tuberculosis and leptospirosis (*Leptospira canicola* and *Leptospira icterohæmorrhagiæ*) are the most important bacterial infections which may simulate aseptic meningitis, because of the lymphocytic reaction of the cerebrospinal fluid and because of the difficulty of early isolation of the organism from the fluid Usually, tuberculous meningitis can be diagnosed on clinical grounds, but leptospiral meningitis often cannot be differentiated from viral meningitis Sera from cases of aseptic meningitis should, therefore, be examined for evidence of leptospiral infection

The serological tests commonly employed by bacteriological laboratories for the diagnosis of leptospirosis are the agglutination and the agglutination-lysis (A L) tests (the latter being considered the more reliable) These tests require darkfield microscopy and are tedious and time-consuming The complement-fixation (C F) test has been recommended for the examination of large numbers of sera for leptospirosis (Schubert and Martin 1956, Terzin 1956) Complement-fixation technique has the added advantage of being part of the daily routine of a diagnostic virus laboratory Leptospiral antigens for use in complement-fixation tests have been prepared from suspensions of inactivated organisms, disrupted organisms, and extracts of organisms (York 1952, Schubert and Carrington 1956, Terzin 1956, Muraschi et al 1956, Rothstein and Hiatt 1956) Of these, the simplest seemed to be Terzin's preparation of crude boiled leptospiral cultures

We have compared the sensitivity and specificity of the complement-fixation test (using Terzin's antigen) with the agglutination-lysis test We also hoped to assess the importance of leptospirosis in the syndrome of aseptic meningitis in the west of Scotland

Materials and Methods

The sera examined came from 250 patients with aseptic meningitis during the period May, 1958, to May, 1960 From most of these patients we received paired sera—i e , one specimen of serum taken during the first week of the illness, and a second specimen taken in convalescence, generally ten to fourteen days after the first For the purpose of this study, the term " aseptic meningitis " includes all cases of non-paralytic illness with pleocytosis of cerebrospinal fluid from which no bacteria were isolated

Agglutination-lysis Tests

These were done by the method of Schuffner (Wolff 1954) using living four day-old strains of *L icterohæmorrhagiæ* (Wijnberg) and *L canicola* (Aldgate), which had been grown in Stuart's medium (Stuart 1946)

Complement-fixation Tests

The same strains of *L canicola* and *L icterohæmorrhagiæ* as employed for the A L tests were used to prepare C F antigens by the method of Terzin (1956) Each strain was grown for twenty-one days in Korthof's medium (Korthof 1932) at 29–30 C, and then incubated for three days at 37 C After being tested for absence of bacterial contamination, the cultures were heated at 100 C for fifteen minutes Flocculation of non antigenic material, which was produced in some cultures by boiling, was removed by centrifugation for ten minutes at 2000 rev per min Sodium merthiolate was added to a final concentration of 1/10,000 of the antigens, which were then stored at −40 C

Type-specific sera were prepared in rabbits by inoculation, at four-day intervals, of 0 5 ml , 0 5 ml , 4 0 ml , and 4 0 ml of whole leptospiral cultures killed with 0 3% formalin Rabbits were exsanguinated seven days after last inoculation Serum was sterilised by Seitz-filtration and stored at 4 C

The optimal dilution of each batch of antigen was determined by chessboard titration against the homologous antiserum The optimal dilutions of both *L canicola* and *L icterohæmorrhagiæ* antigens varied considerably from batch to batch *L canicola* ranging from 1/2 to 1/12, *L icterohæmorrhagiæ* from 1/2 to 1/8 Although there was some cross-reaction between each antigen and the heterologous serum, considerably greater serum titres were obtained with the homologous than with the heterologous antigen—e g , the optimal dilution of *L canicola* antigen gave serum titres of 1/320 and 1/20 respectively with the homologous and heterologous rabbit sera *L icterohæmorrhagiæ* antigen in optimal dilution gave serum titres of 1/320 and 1/80 respectively with the homologous and heterologous sera Both antigens were stable at −40 C for at least three months

The C F tests were carried out in plastic plates with 0 1 ml volumes each of antigen in optimal dilution, serum dilution, and complement (four 50% hæmolytic doses) Dilutions of all reagents were made in barbitone-buffered saline After standing at 4°C overnight, the plates were kept at 37 C for thirty minutes, and then 0 1 ml 2% optimally sensitised sheep cells were added to each cup The plates were left for a further forty minutes at 37°C, and were shaken at fifteen, thirty, and forty minutes, and then allowed to settle at room temperature before reading

Results

Evidence of leptospiral infection was found in 13 (5 2%) of the 250 cases In each of these 13 cases, both A L and C F tests were positive

Comparison of Specificity of the Two Tests

Assuming that the highest titre obtained during the course of the illness is given by the homologous strain, both tests showed agreement on the infecting type-strain in 12 of the 13 cases (see table) *L icterohæmorrhagiæ* appeared to be the infecting organism in case 1, *L canicola* in cases 2–12 The only anomalous finding was in case 13 from whom only one serum was obtained—on the nineteenth day of illness This seemed to indicate infection with *L canicola* by the A L test, but infection with *L icterohæmorrhagiæ* by the C F test The A L result in this case may have been an example of the " paradoxical "

COMPARISON OF AGGLUTINATION-LYSIS AND COMPLEMENT FIXATION TITRES IN LEPTOSPIRAL ASEPTIC MENINGITIS

Case	Age (yr)	Day of illness	Agglutination lysis titres (reciprocals)		Complement fixation titres (reciprocals)	
			L canicola	*L icterohæmorrhagiæ*	*L canicola*	*L icterohæmorrhagiæ*
1	19	6	<10	<10	<8	8
		15	3000	1000	<8	128
		21	3000	30 000	<8	256
		32	300	3000	<8	128
2	20	5	<10	<10	<8	<8
		10	30	<10	64	8
		15	100	<10	64	<8
		27	3000	<10	16	<8
		62	1000	<10	16	<8
3	20	8	100	10	16	<8
		18	300	10	64	8
		32	>30 000	<10	64	<8
4	8	7	300	10	32	<8
		17	3000	10	64	<8
5	34	8	30	<10	<8	8
		28	3000	10	32	<8
6	17	2	<10	<10	<8	8
		14	3000	100	16	<8
7	12	10	300	30	8	8
		18	3000	300	32	16
8	17	17	>30 000	1000	256	<8
		65	3000	30	32	<8
9	12	21	30 000	100	512	16
10	7	21	30 000	1000	512	128
11	13	17	3000	100	256	8
12	22	13	3000	100	256	8
13	9	19	10 000	1000	8	256

otomy revealed numerous hæmangiomas along the small intestine, and a few in the colon Shepherd (1953), in his excellent review of hæmangiomatous conditions of the gastro-intestinal tract, suggested that the lack of reported skin lesions might be due to failure to recognise the association between cutaneous cavernous hæmangiomas and those in the bowel Bean (1958) reported two cases, one a Latin-American girl with skin nævi and bleeding from the bowel, the other a 7-year-old boy who had anæmia, having had skin lesions since he was 3 months old Hæmangiomas were seen on sigmoidoscopy and a resection of the small bowel was necessary because of recurrent bleeding

Appearance of Lesions

The upper limbs and trunk are the commonest sites for lesions, though they may be found anywhere on the skin Unlike Osler-Rendu-Weber disease, the nail-beds are not involved, nor were the lips in any of the reported cases In blue-rubber-bleb nævus disease, the cavernous hæmangiomas are either intracutaneous or subcutaneous, the skin being readily movable over the subcutaneous ones In the arms, they are often close to the superficial veins in the antecubital fossa They vary in size from the 1 mm blue spot to 3–4 cm bunches of cavernous hæmangiomas—the true “ blue-rubber blebs ” which can be partially emptied of blood by firm pressure over the area They may vary in size from day to day Intestinal cavernous hæmangiomas are often submucous, projecting into the bowel and sometimes either occluding or diffusely constricting it (Brown 1924) They bleed readily, and are more common in the small intestine than in the large bowel, they are commoner in the rectum and lower colon than in the proximal half of the colon In our patient, it is possible that the hæmatemesis in 1947 was due to a bleeding hæmangioma, but the operation notes written at the time were too scanty to confirm the presence of an ulcer in the stomach, cutaneous or intestinal hæmangiomas were not remarked upon

Differential Diagnosis

The diagnosis of bleeding intestinal cavernous hæmangiomas is readily made if there are cavernous hæmangiomas on the skin In the Osler-Rendu-Weber syndrome, the usual telangiectasis is a well-defined, flat, depressed, but rarely raised, red or blue spot The telangiectases are to be found commonly on the face and fingers (especially the subungual regions), and nose, as well as in the mouth In the less common nodular type, the lesions are small—1–3 mm in size—and usually occur on the lips, tongue, face, and fingers They never reach the size of blue-rubber-bleb nævi, which are usually raised and are never subungual

Epistaxis is common in Osler-Rendu-Weber disease, but has not been reported in blue-rubber-bleb nævus disease There may be much gastrointestinal bleeding causing a severe iron-deficiency anæmia in both diseases, but the skin manifestations are quite distinct In Maffucci’s syndrome, in addition to widespread cavernous hæmangiomas in the soft tissues, there is dyschondroplasia, giving rise to marked bony deformities

Genetics

Hitherto the mode of inheritance of the combined syndrome of cavernous hæmangiomas of skin and bowel has not been recorded In the family recorded here, five generations are affected by the disease (fig 3), which is clearly transmitted by an autosomal dominant gene There is no evidence of sex-linkage There is no consanguinity in this pedigree, and anæmia has occurred so far in only three members of the family Osler-Rendu-Weber disease is similarly inherited as a dominant trait, although sporadic cases have been known

The uncle, the grandfather, and one brother of the patient died of neoplasms of various organs, this recalls the high incidence of carcinoma in the related state of Maffucci’s syndrome in which there are cavernous hæmangiomas of various organs, accompanied by dyschondroplasia (Johnson et al 1960) In this case there were no bony deformities

Treatment

The treatment of severe and persistent gastrointestinal bleeding in this disease is excision of the intestinal hæmangiomas, if this is possible If surgery is refused or excision is not technically feasible, then injection of the hæmangiomas with sclerosing fluids may be an alternative If bleeding causes chronic anæmia, iron therapy should be advised as a temporary measure, although blood-transfusions may have to be given (Lazarus and Marks 1947) Patients with cutaneous cavernous hæmangiomas only, without evidence of gastrointestinal bleeding, should be watched carefully Hæmoglobin estimations should be done at regular intervals to ensure that intestinal hæmangiomas are not bleeding significantly Trauma to cutaneous nævi may cause moderate blood-loss, but local pressure usually prevents serious bleeding

Conclusions

Blue-rubber-bleb nævus disease is a convenient though dysphonious term for the syndrome of cavernous hæmangiomas of skin and bowel It should be retained because it directs attention to the hitherto seldom recognised skin changes which may give the clue to the cause of gastrointestinal bleeding

Summary

In blue-rubber-bleb nævus disease there are cutaneous and intestinal cavernous hæmangiomas, and bleeding from the intestinal lesions may cause severe anæmia The inheritance of this condition is recorded for the first time the disease is transmitted by an autosomal dominant gene, five generations being affected in the family reported

In patients with gastrointestinal blood-loss, the presence of cutaneous cavernous hæmangiomas should direct attention to the possibility of bleeding cavernous hæmangiomas in the bowel

We are grateful to Dr Raymond Whitehead, reader in pathology, University of Manchester, for the histological report and the photomicrograph We are indebted to Dr R G Ollerenshaw, director of the department of medical illustration, for the photographs of the patient and for the family tree, to Dr Russell Young, under whose care the patient was originally admitted to the psychiatric unit, St Thomas s Hospital, Stockport, and to Prof D A K Black for encouragement and providing facilities for investigation

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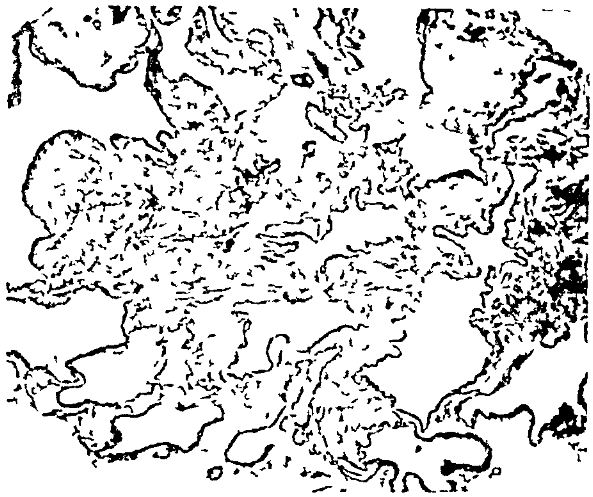


Fig 2—Photomicrograph of cutaneous cavernous hæmangioma showing the large spaces separated by fibrous tissue (low power)

June 10, 1960 Hb 42%(6 2 g per 100 ml)

June 17, 1960 Hb 48% (7 1 g per 100 ml), R B C 4 03 million per c mm , C I 0 59, W B C 7000 (polymorphs 79%, lymphocytes 18%, mononuclears 3%)

June 27, 1960 Intramuscular iron (a total of 22 ml of 'Imferon ') was given over the course of one week

The Hb rose to 68% (10 g per 100 ml), C I 0 79, by June 24, 1960, and, by Aug 8, 1960, was 87% (12 9 g per 100 ml), at which time ferrous fumarate was being taken irregularly by mouth

Wassermann reactions, electroencephalogram, X-ray of chest and skull, liver-function tests, electrocardiogram, and blood-urea were normal

The histological appearance of a biopsy specimen (fig 2) from a lesion on the back was reported thus " The lesion consists of large irregular spaces separated by broad bands of cellular fibrous tissue The spaces are lined by a single layer of flat cells These rest sometimes on a simple or double layer of cuboidal cells, sometimes directly on fibrous tissue Diagnosis cavernous hæmangioma of the back "

The patient refused sigmoidoscopy, barium meal, and enema

Family History (fig 3)

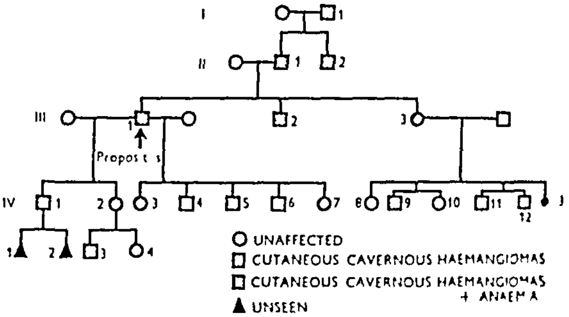
The patient's father, grandfather, and paternal uncle were affected by skin lesions, as were his brother and his only sister The propositus had married twice, both his children of the first marriage and two out of four grandchildren having skin lesions Three out of five of the issue of his second marriage also had cutaneous lesions Three out of four relatives who had skin hæmangiomas died from neoplasms of different organs—brain, stomach, and one the site of which was unknown The father of the propositus one brother, and a sister were known to be chronically anæmic, possibly owing to bowel hæmangiomas

Discussion

Cavernous hæmangiomas of the skin and gastrointestinal tract are responsible for a distinct clinical syndrome, but it is remarkable that they have achieved little recognition as a rare cause of gastrointestinal bleeding

Gascoyen (1860) described a man, with numerous cavernous hæmangiomas of the skin and with anæmia, who eventually died of suffocation due to a hæmangioma in the parotid region McLure and Ellis (1930) recorded recurrent melæna and rectal bleeding in a 30 year-old woman with extensive cutaneous cavernous hæmangiomas Hæmangiomas were present in spleen, liver stomach, duodenum jejunum, and ileum Lazarus and Marks (1947) described a 58-year-old man with profound anæmia due to blood loss Skin lesions suggested the diagnosis of bleeding hæmangiomas of the bowel In the end a lifesaving colectomy had to be done, multiple thin-walled cavernous hæmangiomas were found in the resected colon Lazarus and Marks stressed the importance of recognising skin nævi in gastrointestinal bleeding, as did Holman (1948), who recorded the case of a 9-year-old girl who had large cavernous hæmangiomas of the palm of the hand, suprascapular region, and tongue She suffered from recurrent bleeding and anæmia caused by a cavernous hæmangioma affecting the sigmoid colon

Rickham (1952) described a 10-year-old child who had recurrent melæna, and a cavernous hæmangioma on the palm of the hand A preoperative clinical diagnosis of cavernous hæmangioma of the bowel was made, and, at laparotomy, three small cavernous hæmangiomas were found in the small intestine A similar preoperative diagnosis was made by Heycock and Dickinson (1951) in a 6-year-old girl, with recurrent episodes of anæmia, and hæmangiomas on the chest Lapar-



I
1
II
1
2
III
1
Propositus
2
3
IV
1
2
3
4
5
6
7
8
9
10
11
12
13
V
1
2
3
4
○ UNAFFECTED
☐ CUTANEOUS CAVERNOUS HAEMANGIOMAS
☐ CUTANEOUS CAVERNOUS HAEMANGIOMAS + ANAEMIA
▲ UNSEEN

Fig 3—Family tree of propositus

Males are indicated by squares, females by circles

I —1 Cutaneous cavernous hæmangiomas Died when over 70 from cancer of unknown site

II —1 Numerous cutaneous cavernous hæmangiomas on arms and back Chronically ill and anæmic for years Hæmatemesis in 6th decade Died, aged 65

2 Numerous cavernous hæmangiomas on arms Died, aged 70, from cancer of stomach

III —1 Propositus—see case report

2 Numerous cutaneous cavernous hæmangiomas Discharged from Army because of anæmia Died, aged 42, from brain tumour

3 Numerous cutaneous cavernous hæmangiomas over arms and legs Repeatedly anæmic Now aged 41 Last hæmoglobin whilst under treatment with oral iron 91% (13 9 g per 100 ml)

IV —1 31-year-old man Cutaneous hæmangiomas on arms Not anæmic

2 29-year-old woman with cavernous hæmangiomas on buttocks

3 14-year-old daughter of second marriage of propositus Two skin cavernous hæmangiomas on left knee, one of which was removed and diagnosis confirmed histologically Not anæmic

4 Normal 13-year-old boy No skin lesion

5 11-year-old boy Cavernous hæmangiomas on legs Otherwise well

6 Unaffected 9 year-old boy

7 2-year-old girl with large cavernous hæmangioma on left wrist Painful on pressure Not anæmic

8 Unaffected 13 year-old girl

9 Affected 11-year-old boy Cavernous hæmangiomas on arms Not anæmic

10 Girl twin of IV 9 Died at age of 3 months No record of skin lesions

11 Normal 8-year-old boy

12 Male twin of IV 11 Stillborn

13 Miscarriage

V —1 and 2 Living children of IV 1 Sex unknown

3 8 year-old boy Cavernous hæmangiomas on buttocks Not anæmic

4 5 year-old girl Cavernous hæmangiomas on buttocks and arms

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The upper limbs and trunk are the commonest sites for lesions, though they may be found anywhere on the skin Unlike Osler-Rendu-Weber disease, the nail-beds are not involved, nor were the lips in any of the reported cases In blue-rubber-bleb nævus disease, the cavernous hæmangiomas are either intracutaneous or subcutaneous, the skin being readily movable over the subcutaneous ones In the arms, they are often close to the superficial veins in the antecubital fossa They vary in size from the 1 mm blue spot- to 3–4 cm bunches of cavernous hæmangiomas—the true " blue-rubber blebs " which can be partially emptied of blood by firm pressure over the area They may vary in size from day to day Intestinal cavernous hæmangiomas are often submucous, projecting into the bowel and sometimes either occluding or diffusely constricting it (Brown 1924) They bleed readily, and are more common in the small intestine than in the large bowel, they are commoner in the rectum and lower colon than in the proximal half of the colon In our patient, it is possible that the hæmatemesis in 1947 was due to a bleeding hæmangioma, but the operation notes written at the time were too scanty to confirm the presence of an ulcer in the stomach, cutaneous or intestinal hæmangiomas were not remarked upon.

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The treatment of severe and persistent gastrointestinal bleeding in this disease is excision of the intestinal hæmangiomas, if this is possible If surgery is refused or excision is not technically feasible, then injection of the hæmangiomas with sclerosing fluids may be an alternative If bleeding causes chronic anæmia, iron therapy should be advised as a temporary measure, although blood-transfusions may have to be given (Lazarus and Marks 1947) Patients with cutaneous cavernous hæmangiomas only, without evidence of gastrointestinal bleeding, should be watched carefully Hæmoglobin estimations should be done at regular intervals to ensure that intestinal hæmangiomas are not bleeding significantly Trauma to cutaneous nævi may cause moderate blood-loss, but local pressure usually prevents serious bleeding

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In patients with gastrointestinal blood-loss, the presence of cutaneous cavernous hæmangiomas should direct attention to the possibility of bleeding cavernous hæmangiomas in the bowel.

We are grateful to Dr Raymond Whitehead reader in pathology, University of Manchester, for the histological report and the photomicrograph We are indebted to Dr R G Ollerenshaw, director of the department of medical illustration, for the photographs of the patient and for the family tree, to Dr Russell Young, under whose care the patient was originally admitted to the psychiatric unit, St Thomas s Hospital, Stockport, and to Prof D A K Black for encouragement and providing facilities for investigation.

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SEROLOGICAL DIAGNOSIS IN LEPTOSPIRAL ASEPTIC MENINGITIS

CONSTANCE A C ROSS
M D Glasg
SENIOR REGISTRAR IN VIRUS DISEASES, RUCHILL HOSPITAL, GLASGOW

J C J IVES
M B Edin , F R F P S
TEACHER LECTURER IN BACTERIOLOGY, UNIVERSITY OF GLASGOW, AND CONSULTANT BACTERIOLOGIST, GLASGOW ROYAL INFIRMARY

MOST agents responsible for the syndrome of aseptic meningitis ("lymphocytic meningitis") are viruses Indeed, the virus laboratory now receives far more specimens from cases of aseptic meningitis than does the bacteriological laboratory Tuberculosis and leptospirosis (*Leptospira canicola* and *Leptospira icterohæmorrhagiæ*) are the most important bacterial infections which may simulate aseptic meningitis, because of the lymphocytic reaction of the cerebrospinal fluid and because of the difficulty of early isolation of the organism from the fluid Usually, tuberculous meningitis can be diagnosed on clinical grounds, but leptospiral meningitis often cannot be differentiated from viral meningitis Sera from cases of aseptic meningitis should, therefore, be examined for evidence of leptospiral infection

The serological tests commonly employed by bacteriological laboratories for the diagnosis of leptospirosis are the agglutination and the agglutination-lysis (A L) tests (the latter being considered the more reliable) These tests require darkfield microscopy and are tedious and time-consuming The complement-fixation (C F) test has been recommended for the examination of large numbers of sera for leptospirosis (Schubert and Martin 1956, Terzin 1956) Complement-fixation technique has the added advantage of being part of the daily routine of a diagnostic virus laboratory Leptospiral antigens for use in complement-fixation tests have been prepared from suspensions of inactivated organisms, disrupted organisms, and extracts of organisms (York 1952, Schubert and Carrington 1956, Terzin 1956, Muraschi et al 1956, Rothstein and Hiatt 1956) Of these, the simplest seemed to be Terzin's preparation of crude boiled leptospiral cultures

We have compared the sensitivity and specificity of the complement-fixation test (using Terzin's antigen) with the agglutination-lysis test We also hoped to assess the importance of leptospirosis in the syndrome of aseptic meningitis in the west of Scotland

Materials and Methods

The sera examined came from 250 patients with aseptic meningitis during the period May, 1958, to May, 1960 From most of these patients we received paired sera—i e , one specimen of serum taken during the first week of the illness, and a second specimen taken in convalescence, generally ten to fourteen days after the first For the purpose of this study, the term ' aseptic meningitis ' includes all cases of non-paralytic illness with pleocytosis of cerebrospinal fluid from which no bacteria were isolated

Agglutination-lysis Tests

These were done by the method of Schüffner (Wolff 1954) using living four-day-old strains of *L icterohæmorrhagiæ* (Wijnberg) and *L canicola* (Alderse), which had been grown in Stuart's medium (Stuart 1946)

Complement-fixation Tests

The same strains of *L canicola* and *L icterohæmorrhagiæ* as employed for the A L tests were used to prepare C F antigens by the method of Terzin (1956) Each strain was grown for twenty-one days in Korthof's medium (Korthof 1932) at 29–30 C, and then incubated for three days at 37 C After being tested for absence of bacterial contamination, the cultures were heated at 100 C for fifteen minutes Flocculation of non antigenic material, which was produced in some cultures by boiling, was removed by centrifugation for ten minutes at 2000 rev per min Sodium merthiolate was added to a final concentration of 1/10,000 of the antigens, which were then stored at −40 C

Type-specific sera were prepared in rabbits by inoculation, at four-day intervals, of 0 5 ml , 0 5 ml , 4 0 ml , and 1 0 ml of whole leptospiral cultures killed with 0 3% formalin Rabbits were exsanguinated seven days after last inoculation Serum was sterilised by Seitz-filtration and stored at 4 C

The optimal dilution of each batch of antigen was determined by chessboard titration against the homologous antiserum The optimal dilutions of both *L canicola* and *L icterohæmorrhagiæ* antigens varied considerably from batch to batch *L canicola* ranging from 1/2 to 1/12, *L icterohæmorrhagiæ* from 1/2 to 1/8 Although there was some cross reaction between each antigen and the heterologous serum, considerably greater serum titres were obtained with the homologous than with the heterologous antigen—e g , the optimal dilution of *L canicola* antigen gave serum titres of 1/320 and 1/20 respectively with the homologous and heterologous rabbit sera *L icterohæmorrhagiæ* antigen in optimal dilution gave serum titres of 1/320 and 1/80 respectively with the homologous and heterologous sera Both antigens were stable at −40 C for at least three months

The C F tests were carried out in plastic plates with 0 1 ml volumes each of antigen in optimal dilution, serum dilution, and complement (four 50% hæmolytic doses) Dilutions of all reagents were made in barbitone-buffered saline After standing at 4 C overnight, the plates were kept at 37 C for thirty minutes, and then 0 1 ml 2% optimally sensitised sheep cells were added to each cup The plates were left for a further forty minutes at 37 C, and were shaken at fifteen, thirty, and forty minutes, and then allowed to settle at room temperature before reading

Results

Evidence of leptospiral infection was found in 13 (5 2%) of the 250 cases In each of these 13 cases, both A L and C F tests were positive

Comparison of Specificity of the Two Tests

Assuming that the highest titre obtained during the course of the illness is given by the homologous strain, both tests showed agreement on the infecting type-strain in 12 of the 13 cases (see table) *L icterohæmorrhagiæ* appeared to be the infecting organism in case 1, *L canicola* in cases 2–12 The only anomalous finding was in case 13 from whom only one serum was obtained—on the nineteenth day of illness This seemed to indicate infection with *L canicola* by the A L test, but infection with *L icterohæmorrhagiæ* by the C F test The A L result in this case may have been an example of the "paradoxical"

COMPARISON OF AGGLUTINATION-LYSIS AND COMPLEMENT FIXATION TITRES IN LEPTOSPIRAL ASEPTIC MENINGITIS

Case	Age (yr)	Day of illness	Agglutination lysis titres (reciprocals)		Complement fixation titres (reciprocals)	
			L canicola	*L icterohæmorrhagiæ*	*L canicola*	*L icterohæmorrhagiæ*
1	19	6	<10	<10	<8	8
		15	3000	1000	<8	128
		21	3000	30 000	<8	256
		32	300	3000	<8	128
2	20	5	<10	<10	<8	<8
		10	30	10	64	<8
		15	100	<10	64	<8
		27	3000	<10	16	<8
		62	1000	<10	16	8
3	20	8	100	10	16	<8
		18	300	10	64	<8
		32	>30 000	<10	64	<8
4	8	7	300	10	32	<8
		17	3000	10	64	8
5	34	8	30	<10	<8	<8
		25	3000	10	32	8
6	17	2	<10	<10	<8	8
		14	3000	100	16	8
7	12	10	300	30	8	8
		18	3000	300	32	16
8	17	17	>30 000	1000	256	8
		65	3000	30	32	<8
9	12	21	30 000	100	512	16
10	7	21	30 000	1000	512	128
11	13	17	3000	100	2 6	8
12	22	13	3000	100	2 6	8
13	9	19	10 000	1000	8	2 5

reaction reported by Fühner (1951) in which, during the early stages of the illness, agglutinins for the heterologous strain are higher than for the homologous Cross-absorption tests are then necessary to demonstrate the true infecting strain unfortunately, there was insufficient serum from case 13 for this to be done In this series, a paradoxical reaction was clearly shown by the serial A L results in case 1 on the fifteenth day of the illness, the titres for *L canicola* and *L icterohæmorrhagiæ* were 1/3000 and 1/1000 respectively, whereas, on the twenty-first day, the corresponding A L titres were 1/3000 and 1/30,000 In contrast, the C.F tests in case 1 showed a rising titre for *L icterohæmorrhagiæ*, but not for *L canicola*

Comparison of Titres

There was no consistent correlation between the titres obtained by the A.L. and C.F tests, yet, with the exception of case 3, sera giving the highest A.L titres (30,000 or over) for the infecting strain also showed the highest C F titres (256 or over)

Serial Titres During Course of Leptospirosis

Tests on serial samples were carried out on cases 1–3 It will be seen that the C F test gave an earlier type-specific response than did the A.L. test.

Discussion

The finding of leptospiral infection in 13 (5 2%) of 250 cases indicates that serological examination for leptospirosis is of considerable value in aseptic meningitis None of these 13 patients had jaundice or other clinical signs of leptospirosis A seasonal incidence was noted 8 of the patients with leptospirosis became ill during July to September 5 of the 13 (cases 3, 7, 9, 10, and 11) came from Strathclyde—where there is easy access to bathing in potentially contaminated water

Comparison of the serological results obtained by the C.F and A L tests show that the C F test is as specific as the A.L test Moreover, our finding that the " paradoxical " reaction shown by the A L test in one of our cases was not shown by the C F test suggests that the C.F test for leptospirosis may be more reliably type-specific than the A.L test, particularly in the early stages of illness Besides all these indications of the reliability of the C F test are the overwhelming advantages of the ease of preparation of Terzin's antigen and the eminent practicability of the C F test for the screening of large numbers of sera for leptospirosis

Summary

Sera from 250 cases of aseptic meningitis were examined for leptospirosis by both the complement-fixation test using killed antigens and the agglutination-lysis test with living cultures

Both tests were positive for leptospirosis in 13 cases The complement-fixation test showed a type-specific response earlier in the illness than did the agglutination-lysis test

The ease of preparation, stability, and reliability of Terzin's complement-fixing antigens make them ideal for testing large numbers of sera for leptospirosis

We thank Miss H G Mateer, F I M L T, and Miss C H Gourlay for technical assistance

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ŒSOPHAGEAL CAST

ŒSOPHAGITIS DISSECANS SUPERFICIALIS

A E Stevens
M.B Lond, M.R.C P
MEDICAL REGISTRAR

G A W Dove
M B, B Sc Lond
LATELY HOUSE-SURGEON

CANADIAN RED CROSS MEMORIAL HOSPITAL, TAPLOW, BUCKS

Œsophagitis dissecans superficialis is a rare but benign condition in which the patient vomits a cast consisting of the squamous coat of the œsophagus Patterson (1935) reviewed the eighteen cases published before 1935 Further single cases have been reported by Beck (1954) and Willcox (1949) Barrett (1952) states that some twenty-five have been published Here follows an account of another such patient

Case-report

On March 21, 1958, after a lunch of sausage roll, parsnips, and tea, a housewife aged 34 noticed a burning feeling in her throat as though some food were sticking She swallowed a piece of bread hoping that this might relieve the symptom, but it did not. Later in the afternoon, she retched and brought up a little bright-red blood, followed by " something like string ", which hung out of her mouth She was unable to remove the " string " as it was attached below, and traction on it caused burning pain over the upper sternum She became frightened and came to the casualty department Fig 1 shows her appearance The cord was composed of a tough translucent substance, and, when pulled, the pain described was reproduced There was neither koilonychia nor smooth tongue

After some deliberation on the part of the assembled resident staff, the " cord " was cut as low down as possible, and the attached end allowed to slide back down the patient's throat Subsequently, a history was obtained of two previous episodes of burning sensation in the throat, six months and three months

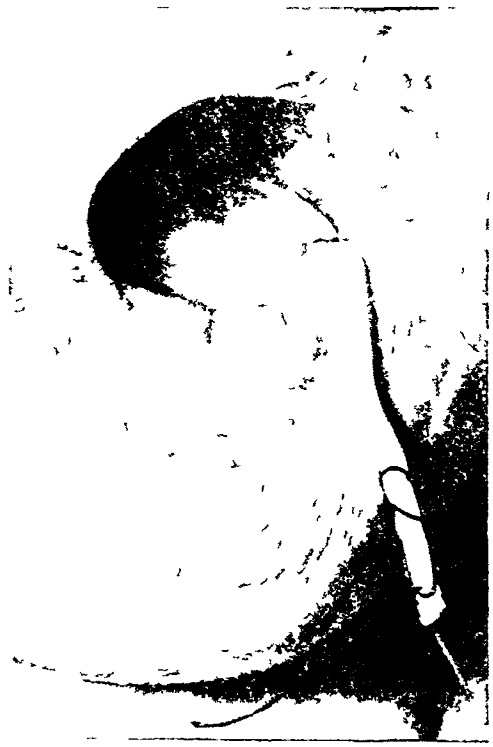

Fig 1—Cast in situ on admission

before During each episode, which lasted about a week, the throat felt " as though it had been scratched by some food " There had been no further symptoms on either occasion. In spite of the unappetising-sounding meal before admission, the diet was usually normal, although the patient had a poor appetite No caustic had been swallowed There was a history of iron-deficiency anæmia and pulmonary tuberculosis

Investigations —The cast measured 20 cm , and, on section, it was a tube of stratified squamous epithelium, typical of the lining of the œsophagus The whole thickness of the epithelium appeared to have been shed No inflammatory cells were present, although occasional basal cells showed ballooning (fig 2)

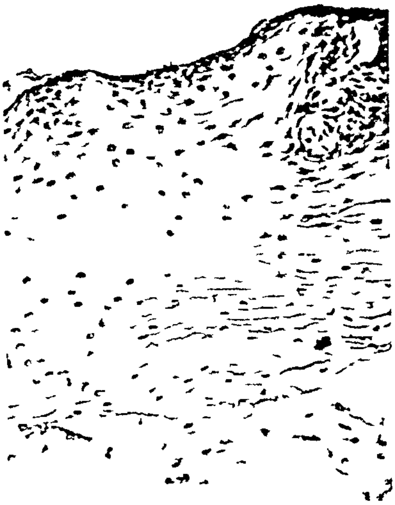

Fig 2—Section of portion of cast (×120)

Hæmoglobin 8 0 g per 100 ml (54%), leucocyte-count 4600 per c mm (polymorphs 84%, lymphocytes 10%, monocytes 6%) Blood-film, moderate hypochromia, anisocytosis, occasional polychromatic cells Sternal marrow-puncture, normal Histamine test-meal, no free acid present Chest X-ray, calcified foci at both apices and right hilum Wassermann reaction (W R), positive, Kahn, doubtful

Treatment and progress —During the week after admission, the patient's temperature was raised intermittently to between 99° and 100°F Her initial dysphagia subsided under treatment with amethocaine lozenges and sedatives, aided by a bland diet The possibility of mediastinal infection was feared, and the patient was given a five-day course of 1 2 million units of procaine penicillin with 1 g of streptomycin daily The anæmia was treated with a two-pint blood-transfusion, followed by oral iron Barium swallow two weeks after admission showed normal œsophageal mucosa Except for an admission in February, 1959, for bronchopneumonia, the patient has remained well

Discussion

This patient also suffered from inactive pulmonary tuberculosis and iron-deficiency anæmia—neither of which have been a feature of previous cases

There was some doubt about the interpretation of the positive W R , especially since a routine antenatal W R , in 1953, had been negative The serological technique of our own laboratory was checked and found to be satisfactory, and a series of tests (in which the Venereal Diseases Reference Laboratory kindly cooperated) was carried out (see table) The serological examination of the patient's husband was negative

It is hard to say whether the serological findings in this patient are relevant, evaluation is complicated by the course of penicillin immediately before the first test Probably these reactions were non-specific, this hypothesis is supported by the negative treponemal immobilisation tests (Kostant 1956) Such reactions have been noted in many conditions, including active tuberculosis and anæmia (Moore and Mohr 1952) Patterson (1935) states that in none of the cases he reviewed was there any indication of syphilitic taint " and the W R in his own patient, and in that of Willcox (1949), was negative

SEROLOGICAL INVESTIGATIONS

Occasion	Date	Test	Result
Routine antenatal examination	Feb 2, 1953	W R	–
		Kahn	–
Admission (œsophagitis dissecans superficialis)	March 21 1958		
	March 27	W R	–
		Kahn	Doubtful
	April 3	Treponemal W R	–
		Standard W R	–
		P P R	–
	April 11	W R	+
		Kahn	+
	April 28	T P I	–
	May 14	T P I	–
		W R	–
		Kahn	–
Admission (broncho pneumonia	Jan 21 1959		
	March 2	W R	–
Follow up examination	Feb 15, 1960	W R	–
		Kahn	Doubtful

W R = Wassermann reaction
P P R = Price s precipitation reaction
T P I = Treponemal immobilisation test

Our patient is in every other way typical of those previously described, including the common history of a meal at which the patient took a hot drink immediately before the onset

Presumably the lack of significant bleeding, and absence of shock or any late complications, are due to gradual separation of the cast, with the formation, deep to it, of a new layer of squamous tissue, so that the cast is finally attached by a few vascular strands only This, and other speculations about ætiology, are discussed by many of the authors mentioned, including Patterson (1935) and Barrett (1952)

Summary

A further case of œsophagitis dissecans superficialis is described in which a probably non-specific positive Wassermann reaction was present

We are indebted to Mr Raymond Ramsay for permission to publish an account of his patient, to Dr A E Wilkinson of the Venereal Disease Reference Laboratory for his assistance, and to Mr Peter Fiske, of the photographic department, Canadian Red Cross Memorial Hospital, for the illustrations

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" developments of the kind I have mentioned as occurring in Britain have occurred quite as effectively and sometimes more so in other countries under systems quite different from that of the British National Health Service Very little reflection soon led to the conclusion that the problems are essentially the same everywhere The next thought, however, was that we are all working on them more or less in isolation Knowledge of what is happening in other countries is casual and often very incomplete and even inaccurate Furthermore, there exists no convenient or ready means of obtaining this information I believe it would be well worth while to start trying to supply this want What I have in mind is an information or intelligence service which could collect and collate accurate information on the subject from as many sources as possible, and perhaps in time initiate studies on various aspects of it It seems to me that this is a project which the Commonwealth is admirably suited to initiate" —Dr I R C WALLER *Practit* , October, 1960 p 205

COEXISTENT PULMONARY COCCIDIOIDOMYCOSIS AND TUBERCULOSIS

GERALD B. REAMS *
Captain, U.S.A.F. (M.C.)
CHIEF, SURGICAL SERVICES,
7510TH U.S.A.F. HOSPITAL, WIMPOLE PARK, ENGLAND

WITH the great increase in transcontinental travel, various diseases—although endemic in only a small section of the world—can now be found everywhere (Nabarro 1948, Smith et al. 1957, Riddell and Clayton 1958). Coccidioidomycosis is such a disease. It may be present at the same time as other forms of pulmonary disease (Hauser and Glazer 1950, Hedberg et al. 1951, Shefran and Karie 1955, Chyley 1956, Ellman and Hanson 1958, Patel and Anand 1959, White et al. 1959) and the following case presents an interesting pathological combination.

Case-report

A man, aged 22, was first seen in March, 1959, because of an abnormal chest X-ray. Mobile-unit microfilms in 1957 and 1958 were reported as normal, though he had been told to see his doctor after a microfilm in July, 1956.

He had grown up in the San Joaquin Valley in California—an endemic centre for coccidioidomycosis. He arrived in Britain in November, 1958. There was no history of tuberculosis or known contact with anyone suspected of tuberculosis.

He was in excellent physical condition and did not complain of malaise, weight-loss, anorexia, night-sweats, chest pain, cough, or hæmoptysis. The blood-pressure was 120/78 mm. Hg, pulse-rate 80, weight 180 lb., and height 6 ft. There was some increase in vocal fremitus over the apex of the right lung, but the chest was otherwise normal on auscultation and percussion.

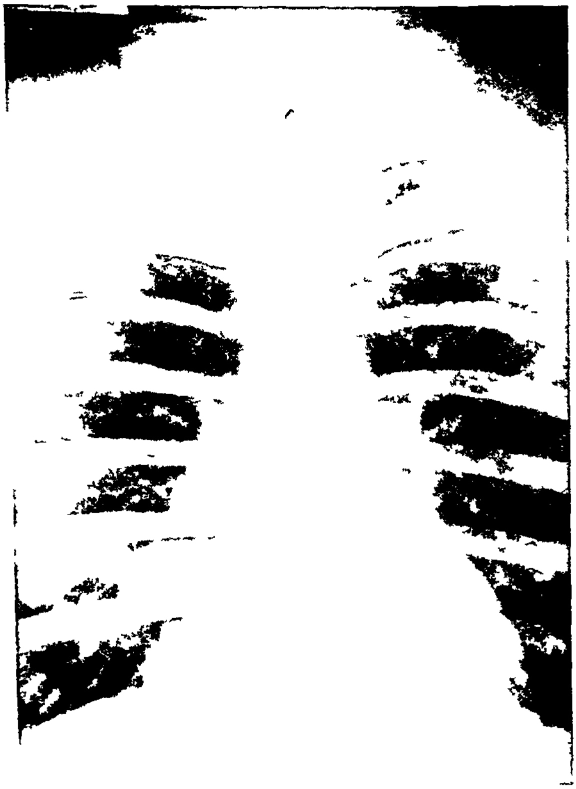

Fig. 1—Chest radiograph showing suspicious area in right apex.

A chest radiograph (fig. 1) and a tomogram of the suspicious area in the right apex (fig. 2) showed a pulmonary infiltration consisting of fibrotic and calcific patches with a number of softer-appearing areas in the right apex which were thought to represent recent activity. The purified protein derivative (tuberculin) test and the coccidioidin skin test were positive, the histoplasmin skin-test was negative. The vital capacity was 4800 c.c., with a breath-holding duration of 52 seconds. Coccidioidin precipitin and complement-fixation antibody titres were not significant.

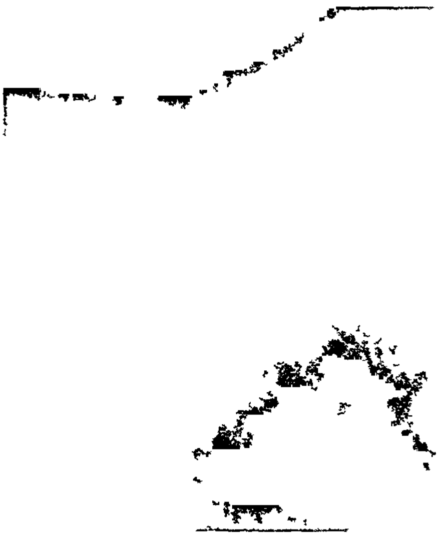

Fig. 2—Tomogram of the right apex.

Bronchoscopy showed no evidence of endobronchial lesions, and bronchial washings were negative for acid-fast and fungus organisms, the cytological examination showed no abnormalities. A right supraclavicular fat-pad biopsy was performed, the nodes showed reticuloendothelial hyperplasia. Complete bacteriological examination on this specimen was negative. Since it was felt that a diagnosis could not be made on this infiltrate without lung biopsy, the patient was prepared for a further operation by a two weeks' course of streptomycin and

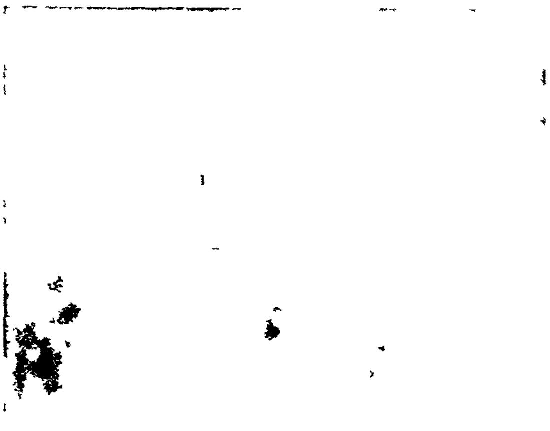

Fig. 3—Coccidioidomycotic spherules in lung. (×200.)

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* Present address: U.S.A.F. Hospital, Keesler Air Force Base, Mississippi.

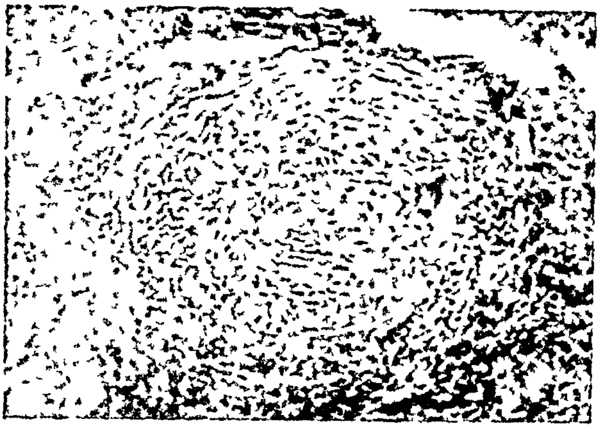

Fig 4—Tuberculous granuloma of lung (×25)

p-aminosalicylic acid (P A S) A right apical segmental resection was done, since all the palpable disease was confined to this area Examination of the resected specimen revealed an area showing the doubly refractive spherules characteristic of coccidioidomycosis (fig 3), as well as a separate caseating granulomatous pneumonitis containing acid-fast organisms, proved on culture to be *Mycobacterium tuberculosis* (fig 4)

The patient's postoperative course was excellent with complete lung re-expansion, and good return of pulmonary function to preoperative levels

P A S and isoniazid therapy was continued, and the patient gradually returned to full duty Nine months after the surgical procedure, there was no evidence of any recurrence of the disease, either clinically or radiologically

Discussion

Coccidioidomycosis is a fungus disease, endemic in the south-western United States, north-western Mexico, and some Central American countries The fungus itself is diphasic, having vegetative and spore phases In its vegetative phase, it consists of long thin mycelia which segment and form highly infective chlamydospores The initial infection occurs by the inhalation of dust contaminated by these chlamydospores In the lungs, they develop into doubly refractive spherules which reproduce by endosporulation (Forbus and Bestebrevvtje 1946, Peterson et al 1948, Pittman and Kane 1951, Baum and Schwartz 1955, Fiese 1958) *This initial pulmonary* infection usually subsides without sequelæ A rare form disseminated by the blood-stream has an approximately 50% mortality-rate In about 10% of the patients there are residual lung lesions which may become solid discrete soft granulomatous areas, or which may cavitate and resemble the lesions of tuberculosis (Altmeier and Culbertson 1957, Merendino 1957) A history of having visited or travelled through an endemic area suggests the correct diagnosis, especially when the coccidioidin skin-test is positive Diagnosis is confirmed by finding the organism in the sputum, in local discharges, or in biopsy material (Salvin 1959)

The acute form is difficult to treat with any form of therapy intended to raise the resistance of the body to the organism Amphotericin B is under investigation as a chemotherapeutic agent, but its value is still undetermined (Hyde 1958, Littman et al 1958, Seabury and Dascomb 1958, Winn 1957 and 1959) There seems to be little danger of reinfection from these residual lesions and surgery is usually reserved (1) for cavities over 4 cm in diameter, or for those enlarging, (2) for recurrent hæmoptysis, (3) for secondary infection, or (4) for the complications of cavity rupture In endemic areas, solid discrete pulmonary lesions are quite common and are usually kept under observation by periodic radiography, since excision of all " coin lesions " would be impracticable In non-endemic areas, lesions are usually excised, to aid accurate diagnosis, since differentiation from an early bronchogenic carcinoma or tuberculosis may not always be possible Lobectomy is usually the procedure of choice because of the presence of satellite granulomas, undiagnosed by radiography This operation should not be regarded as curative any more than it is in tuberculosis (Grier et al 1949, Cotton et al 1957, Merendino 1957, Melick 1957, Timmes and Baum 1957, Hyde 1958, Goldman 1959, Small 1959) Before surgery, ascertainment of bronchiectasis, and accurate location of the cavity by endoscopy and radiography, are necessary (Birsner 1954, McCarthy and Misra 1959) Postoperative dissemination is negligible, early ambulation and return to work in about a month is usual (Goldman 1959)

Summary

A young white man without symptoms was found to have a right upper lobe pulmonary infiltration which could not be definitively diagnosed on the basis of skin tests, sputum studies, bronchoscopy, or supraclavicular fat-pad biopsy A segmental resection revealed the lesion to be the effect of coexistent coccidioidomycosis and active pulmonary tuberculosis

This is thought to be the first reported instance of this combination in England

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" a peculiarly revealing inconsistency does not appear to have received any attention When the pathologist of one hospital examines sections of tissue removed from a patient and expresses an opinion on the character of a lesion or the identity of a tumor, his opinion is accepted by the other members of the staff But if the same patient should subsequently be admitted to another hospital, the opinion of the first pathologist is not accepted Thus, the phase of pathology that is commonly known as microscopic pathology rests partly on the faith *of physicians who rely on a particular pathologist* This kind of faith often depends on the pathologist's personality, and some pathologists impress their personalities on others to such a degree that their opinions acquire the prestige of dogmas "
—ARTHUR U DESJARDINS, M D , *Arch intern Med* 1960, 105, 596

Reviews of Books

The Mentally Subnormal

The Social Case Work Approach Editor MARGARET ADAMS, social worker, mental-health services, London County Council London William Heinemann 1960 Pp 271 25*s*

Social Rehabilitation of the Subnormal

HERBERT C GUNZBERG, PH.D , F B PS S , consultant psychologist, director of psychological services, Monyhull Hospital, Birmingham London Bailliere, Tindall, & Cox 1960 Pp 263 27*s* 6*d*

THE new Mental Health Act will turn the attention of many people besides doctors towards various types of mental abnormality It is to be hoped that mental deficiency, now legally known as subnormality, will not be the least important The subject has been quietly ignored by many for generations, to an extent which suggests strong unconscious resistances for we can scarcely deny its importance in extent and in intensity, in clinical work and social. It took the Royal Commission's findings to point out that much more could be done for defectives, even under the old Acts We therefore welcome wholeheartedly a number of new textbooks, and especially these two which deal with the social problems of the defective With many patients discharged already under the first reviews, there is increasing pressure on social workers to learn more of the subject, for hospitals, general practitioners, and relatives will all be making demands on their services

Mrs Adams must be congratulated on her vision and energy in persuading a set of eminent contributors to produce *The Mentally Subnormal* Dr Kenneth Soddy's description of the clinical picture stands out for its clarity and conciseness, and the three last chapters on employment and occupations (Dr A. M Clarke, Dr A D B Clarke, and Mrs Adams), social research (Dr J Tizard), and training (Miss K McDougall) all describe recent work and the present situation in a way that stimulates thought about the needs of the future There are also clear accounts of the history of the subject, and we are reminded (as we need to be) of the success of training centres and home education

The descriptions of the general principles of casework, and of various types of work in the community and in the hospital are less successful, being too repetitive Much of what is said here on parental reactions and their treatment has been already covered more simply and concisely in Dr Soddy's chapter No doubt the precise role of the social worker needs amplifying, and this should be a very important part of the book, but chapters III, IV, and VI (which occupy half the pages) need recasting for future editions, which we hope will follow As Dr Tizard puts it elsewhere, " the problems of counselling and of communication generally need a lot more study ", and this applies to parts of this book.

Dr Gunzburg's book is a much deeper view of a narrower part of the subject it is essential reading for anyone directly concerned in the education and training of the subnormal Naturally, the author describes the programme of rehabilitation carried out by his colleagues and himself, and he derives the principles set out here from his considerable experience His book will be a classic for the few engaged in detailed work of this kind But it has a wider appeal, and can be cordially commended to the many, in society and in industry, who need to understand the mind and behaviour of the subnormal It is disturbing to reflect that certain chapters, notably those on counselling and on occupation and training, can certainly be read with profit by people who have to manage normal firms and companies, for they will readily recognise the behaviour disorders and failure of communication here described as " subnormal " This will not, of course, surprise Dr Gunzburg, who emphasises elsewhere that performance on tests is due as much to emotional reactions of the moment as to intellectual capacity—a point curiously hard for managers, trainers, and even psychologists to act upon

These two books should be read in conjunction, for whereas Mrs Adams' was written from the social worker's viewpoint, Dr Gunzburg sees things from the patient's angle The only criticism is that occasionally he seems to ignore the patient's effect on society The idea of a subnormal person gaining a driving licence, before he can read any of the Highway Code or more than a few road signs, will raise eyebrows, if not goose-flesh Yet the author's optimism, persistence, and detailed programme are necessary if we are at last to discard the idea of the incurable unemployable defective

Interpersonal Relationships in the Hospital

WARNER F BOWERS, M.D , M SC , PH.D , chief, general surgery service, Tripler U S Army Hospital, Honolulu Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1960 Pp 125 40*s*

PERHAPS this little book might best be described as a medical *How to Make Friends and Influence People* Written as a sort of extended essay by an unusually perceptive surgeon, it describes and illustrates how relationships go wrong between doctors and their colleagues, their patients, patients' relatives, subordinates, and administrative staff, and it offers much excellent practical advice on various neglected aspects of hospital life and practice It may be rather tilted towards litigation (and its avoidance), for this seems much commoner in the U S A., where Dr Bowers believes that 90% of doctors sued are not guilty of technical error Legal action represents the ultimate in the destruction of the doctor/patient relationship, and undoubtedly a wiser approach to the patient and his family would avoid a great many actions The chapters on malingering and what to say to a patient with a fatal disease are particularly sound, though when he discusses how to present " sensitive " data before patients on teaching rounds he might have advised his readers to retire and discuss the case in private. Some comments on fees and insurance benefits are happily of scant relevance in this country, and the liberal sprinkling of earnest quotations from Confucius onwards become irritating Again, the author is not quite at his best in his classification of people troubled by disorders of mind or personality who come (or want to come) for surgery

Though little that Dr Bowers says is new, and much of it is just common sense, these are things that cannot be said too often, and we recommend the book for compulsory reading during the pre-registration year

The Detection of Secret Homicide

A Study of the Medico-legal System of Investigation of Sudden and Unexplained Deaths J D J HAVARD, LL B , M.B , barrister-at-law, Middle Temple Edited for the Institute of Criminology, University of Cambridge, by L RADZINOWICZ, LL.D London Macmillan 1960 Pp 253 35*s*

BEFORE a murder can be solved it must be discovered, and this scholarly book deals in considerable detail with the ways in which a murder may be exposed and brought to the notice of investigating authorities The development of the English medicolegal system of dealing with sudden and unexpected death is traced from the 12th century to modern times a survey of absorbing interest, throwing a searching light on social conditions and moral outlook in earlier ages when the murder of adults and children, sometimes for trifling profit, was known to be common, even though many cases must have remained secret Emphasis is given to the apathy and recurrent antagonism which seriously retarded the development of the system, despite the great need for increased safeguards of life, but gradually prejudice was overcome and the worst defects were rectified.

The account of the contemporary situation, however, shows that there is still little justification for complacency it can be very easy to have a death certified as " natural ", and the death of a chronically ill patient at first certified as natural has often later been found to be due to deliberate or accidental violence This is disturbing reading, especially in conjunction with a later remark that more than 100,000 bodies a year are buried without being seen after death by a doctor One chapter is concerned with the necessity for expert necropsy after sudden or unexplained death, because many murders were initially overlooked, either because there was no necropsy or because the body was examined by someone inexperienced in medicolegal work The remark in this chapter that necropsies for coroners in London are always carried out by forensic pathologists is incorrect Much attention is given to the certification and registration of deaths, including the problems involved in stillbirths, and the channels along which information can reach the coroner

A highly critical approach is maintained throughout this book, but the final chapter suggests remedies for many of the present weaknesses Among these suggestions are a comprehensive reorganisation of the coroner system, improvement of the certification and registration of death, more direct and speedier reporting to the coroner, safeguards for cremation, burial at sea, and embalming, and tighter regulations concerning stillborn infants

The book is very well documented and errors are few An intricate topic has been most carefully and lucidly presented, and there is much here to stimulate thought in anyone whose ambit includes medicolegal affairs

Law for the Rich

A Plea for the Reform of the Abortion Law ALICE JENKINS With a foreword by GLANVILLE WILLIAMS, LL D , F B A London Victor Gollancz 1960 Pp 95 15*s*

IN this short book written, she tells us, in her 72nd year, Mrs Jenkins describes the efforts of what Dr Glanville Williams calls a pressure-group to secure reform of the law against abortion Of the group's humanity, courage, patience, and devotion there can be no question and it takes some hardihood to deny that the existing law—unequal, at once terrifying and ineffectual, and part cause of the great sum of misery, impaired health and lost lives associated with illegal interference with pregnancy—needs reform What to put in its place is a far more difficult question

This group—the Abortion Law Reform Association—believes that a pregnant woman should have the right to decide whether her pregnancy should go to term, and, though a far more moderate Medical Termination of Pregnancy Bill, drafted by Dr Glanville Williams, appears in an appendix the group apparently regards it as only an interim measure It remains to be seen what they think of Mr Kenneth Robinson's Bill which will have a second reading on Feb 10

Neither Mrs Jenkins nor Dr Glanville Williams seems quite to realise what the practical implications of their proposed reforms are If the present law is to be changed, someone must be given life-or-death power over the conceived unborn until a certain time after conception How long shall this time be? How shall it be determined and who shall decide? The pregnant woman, husband and wife, a tribunal, one doctor or more than one, are possible candidates and there are obvious objections to any or all At present the doctor practises on the basic principle that he does not take life (save exceptionally to save life), to ask him to depart from it is not a small matter and, for the sake both of the common good and of the profession of medicine, the conditions under which he does so depart must be very clearly defined

Space Biology

The Human Factors in Space Flight JAMES HANRAHAN , DAVID BUSHNELL London Thames & Hudson 1960 Pp 263 35*s*

WHENEVER America or Russia sends a new device out of the atmosphere, some newspapers discuss what they call the "space race This new book from America has won another sort of race the race to get an account of the human factors in space flight" into print, and it bears some signs of hurried preparation No doubt there were competitors in hard pursuit

Despite a chapter on philosophy, religion, education, music, painting and literature, the book is largely a catalogue of the events experiments and personalities of the American effort in space research The authors are to be congratulated on their energy and tenacity they have collected all relevant (and some not entirely relevant) pieces of information on the subject, and they seem to have included the full names of any of their countrymen who have done anything said anything, or written anything about space This punctiliousness sometimes makes dull reading, but it serves to balance the racy journalistic style of the writing Nevertheless, the book is a useful up-to-date summary of progress in the new exploration, especially since it contains almost every possible reference in easily readable form

It is impossible to read this account without marvelling at the immense efforts Americans have made to solve the scientific, technological, and biological difficulties that face them The number of commercial firms, universities, service institutes, laboratories, and other Government agencies partly or wholly engaged on space research is remarkable, and the single-minded determination and courage of some of the experimenters commands the greatest respect Many of the ideas and the suggested solutions seem farfetched for example, the proposal that, like Hansel and Gretel, the space traveller should keep alive by nibbling portions of the ship, the internal structure of which is to be entirely edible, or that, to protect him against the effects of acceleration, he should be entirely immersed in the liquid rocket fuel Yet many were inclined to mock at attempts to intercept, in a net drawn by an aircraft, an object falling through the skies above the Pacific—a catch which, after many failures, the Americans have twice brought off

The book gives all the facts about space and how to get ready to explore it For the general medical reader (or his son just entering medical school) it is an inexpensive and unexacting way to prepare for and understand the next exciting steps in the exploration of the universe

Behavior Genetics

JOHN L FULLER, Roscoe B Jackson Memorial Laboratory, W ROBERT THOMPSON, Wesleyan University New York and London John Wiley 1960 Pp 396 72*s*

THE two American authors have each had wide experience of research into the genetics of intelligence and behaviour in lower mammals, such as dogs, rats, and mice In this valuable work they set out what is known of the inheritance of human intellectual abilities, personality and temperament, and mental disorder against this background of experimental work in animals There is substantial agreement between the animal findings and the human data in showing that genetic factors contribute much to the variation found in mental qualities Unfortunately, the animal experiments as yet add little to our understanding of the genetic mechanisms involved

The Practice of Medicine (2nd ed London J & A Churchill 1960 Pp 973 37*s* 6*d*)—The second edition of this popular textbook is a notable achievement Not only has Sir John Richardson been able to make it slightly shorter than the first, but he has reduced its size and thickness so successfully that it now weighs only about $3^{1}/_{2}$ lb instead of its old weight of $7^{1}/_{2}$ lb This slimming process is much to be welcomed, especially since the fat has, as it were, been taken off where it was least wanted Certain sections have been reduced, but the policy has been that where a subject is well known less space has been given to it than where several possibilities have to be discussed The only question here, of course, is to decide by *whom* the subject is well known if the reader is a medical student at the beginning of his clinical medicine he may at times feel the need for amplification This possible complaint is, however, well compensated for by the clear style of most of the writing, and the generally practical and decisive attitude which nearly all the authors have adopted There is a new section on fungus diseases of the lungs, and references to much new work More emphasis might usefully be given to ischæmic heart-disease and atherosclerosis, compared, say, with chronic valvular disease of the heart, and less perhaps to syphilis, which has more pages than both the first two conditions combined even without including central nervous lesions But these are matters of opinion and do not detract from the value of this competent and useful book, for which the editor, authors, and publishers deserve much credit

THE LANCET

LONDON 10 DECEMBER 1960

Genetic Hazard of Medical X Rays

DISQUIET over the possible genetic effects of medical radiology was aroused by the Medical Research Council's report[1] in 1956, and soon afterwards the then Minister of Health announced the formation of a committee, with Lord ADRIAN as chairman, to "review the present practice in diagnostic radiology and the use of radiotherapy in non-malignant conditions and to make recommendations" The committee found their task long and involved Their interim report[2] last year dealt with mass miniature radiography, and the second report,[3] published this week, analyses the genetic hazards of medical radiology, the somatic hazards are still under study, and presumably a further report on these will follow

The committee's main conclusion is that there is no need for major restriction in radiological practice They estimated the annual genetic dose to the population of this country—i e., the dose which would have to be given to everyone to produce the same genetic effect as the doses actually received. Medical diagnostic radiology contributes an annual average of some 14 milliroentgen (mr) per person, compared with "at least 22" estimated in 1956[4], and therapeutic radiology adds just over 5 mr, for which there is no previous figure for comparison These values are undoubtedly much more reliable than earlier estimates, the accuracy being put at better than ±10% The reasons for this precision include the fact that statistical data were obtained from the 1500 hospitals of the National Health Service which have X-ray equipment, thus enabling the distribution of examinations between the different types and the various age-groups of patients to be determined more accurately than before An idea of the scope of the work behind the report can be given by some figures in 130 hospitals, about 60 physicists carried out 13,800 measurements of the radiation received by over 5400 patients This is a much vaster survey of radiation dose than any so far attempted anywhere in the world, and the variations of technique and dose that were found between one hospital and another fully justify the scale of this inquiry

In male patients the dose to the scrotum was measured directly, but in females estimates of skin dose were made in the centre of the X-ray beam and over the ovary, an electronic computer converted these to ovary doses, using a series of measurements carried out on a model designed to absorb and scatter X rays in the same way as a human body For many types of examination the mean values of gonad dose per examination thus derived are similar to those previously reported[5–7] For some, such as pelvimetry and salpingography, the dose now reported is lower than earlier figures, and this may reflect the publicity of the past few years about possible hazards of obstetric and gynæcological radiology Other examinations, such as chest radiography, show a high average, because in some hospitals techniques were poor and the gonads were in the primary beam, indeed, the gonads were in the beam for 10% of all chest radiographs of males recorded in detail, and for as many as 51% of those for females Consequently, radiology of the chest provides as much as 5% of the genetic dose due to diagnostic radiology Obstetric radiology contributes a third of the total, and irradiation of the pelvis and femur another third Separate surveys of mass miniature radiography of the chest and of dental radiography showed that these each contributed only about a thousandth of the annual genetic dose Of the much smaller dose from radiotherapy, only 10% is attributable to the treatment of malignant disease, partly because patients are often sterilised by the treatment, and partly because they are older and therefore less likely to have children More than half the total radiotherapy dose comes from the treatment of skin conditions, and most of the remainder from the treatment of ankylosing spondylitis Only a small proportion of the total can be attributed to radioactive isotopes used in diagnosis and therapy

Two striking points emerge from the dose survey Firstly, the gonad dose in diagnostic radiology is not necessarily reduced by making the beam of X rays more penetrating an optimum is reached at about 70kV with 1 mm of aluminium filter Secondly, a few hospitals with faulty techniques can contribute a large fraction of the total genetic dose, and the same is probably true for the radiotherapy of non-malignant conditions It is estimated that the total annual genetic dose of 19 3 mr could probably be reduced to about 6 mr, simply by the universal adoption of careful techniques giving low doses to the gonads A similar point was made, in a less striking way, by LARSSON[8] in his assessment of the genetic dose in Sweden

In the report several specialist panels make many useful suggestions about how the dosage could be reduced without affecting the value of radiology in the various specialties, and they deserve careful study The main recommendations (summarised on p 1292) are clear and forthright, but not very revolutionary, and they are similar to those of committee III of the International

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[1] Hazards to Man of Nuclear and Allied Radiations H.M Stationery Office 1956 Cmd 9780

[2] Committee on Radiological Hazards to Patients Interim Report. H M Stationery Office 1959 See *Lancet* 1959 i 975

[3] Radiological Hazards to Patients Second Report of Adrian Committee H.M Stationery Office. 1960 Pp 114 6s

[4] Osborn, S B Smith E. E. *Lancet* 1956 i 949

[5] Stanford R. W Vance, J *Brit J Radiol* 1955 28 357

[6] Martin J H *Med J Aust* 1955 ii 806

[7] Laughlin J S Meurk M L Pullman I Sherman R S *Amer J Roentgenol* 1957 78 961

[8] Larsson L. E. *Acta radiol* suppl 157, 1958

Commission on Radiological Protection [9] Most of them are already observed in the best radiological departments, but their universal adoption will cost effort and money, we hope that both will be amply provided For instance, light-beam diaphragms are recommended, gonad shields "should invariably be used" where a high gonad dose can be prevented by their use, image intensification should be more widely used, all equipment should be checked regularly, and the development of automatic devices encouraged, adequate medical and technical staff should always be available, and suitable training given in radiological hazards It is certainly going to be hard to supply enough well-trained radiographers to staff fully every X-ray department in the country And if, as seems very likely, it is impossible without a big increase in their salaries, the money must be provided A smaller point of interest is that the localisation of metal foreign bodies by fluoroscopy is deprecated because "electronic metal-locating equipment is now available" Such equipment has been described from time to time,[10] but is, we believe, available commercially only from America, we hope that similar British-made apparatus will be on the market before long

Most of the recommendations, however, will cost little more than careful thought to implement Previous X-ray examinations or courses of radiotherapy should be investigated before a patient is further exposed to radiation, the X-ray beam should be of the minimum practicable dimensions and when possible should be diverted away from the gonads, fluoroscopy should be replaced by radiology whenever possible, and should in any case be preceded by ten minutes' dark adaptation, fast films and screens should normally be used Of these measures, undoubtedly the most important is reduction of the size of X-ray beams to the minimum necessary, and the authoritative re-statement of this point in the report should carry great weight

Lord ADRIAN's committee, and those who have worked with them, are to be congratulated on the monumental task described in their second report They have contributed to a better understanding of how the benefits of radiology can be enjoyed in our generation without serious risk of accumulating genetic debts for our descendants to pay While the genetic dose from radiology is smaller than was at one time feared, and is smaller than that in many other countries, it is, as the report remarks, much greater than necessary and should therefore be reduced They have thus skilfully contrived to reassure the general public about X-ray examinations while admonishing those radiologists and, more especially, other doctors who do not ensure that adequate precautions are taken to protect their patients as well as themselves and their staff We hope the Adrian recommendations will be promptly followed by hospitals and doctors with X-ray equipment, without the need for regulations or legislation

Chemoprophylaxis in Chronic Bronchitis

THE first recognisable pathological change in chronic bronchitis is hyperactivity of the bronchial mucous glands,[1] which clinically is reflected in viscid, grey sputum, but sooner or later pathogenic organisms are apt to gain a foothold in the bronchial tree and infection may become an important factor Acute episodes require prompt treatment, first, because they may produce sudden, disastrous deterioration of lung function, and, secondly, because residual bronchopulmonary damage should be minimised in order to prevent further permanent encroachment on the respiratory reserve MULDER's original work,[2] since amply confirmed,[3-8] indicated that the pyogens most commonly associated with infection in chronic bronchitis and bronchiectasis are *Hæmophilus influenzæ* and the pneumococcus, and it is now accepted practice to prescribe in the first instance chemotherapy effective against both these organisms—a combination of penicillin with streptomycin, chloramphenicol, or one of the tetracycline group of drugs

But, if it is good to cut short acute episodes of infection, it is obviously better to prevent them, and several workers have investigated the possibilities of chemoprophylaxis Streptomycin must be given by intramuscular injection, and long-continued chloramphenicol administration may produce blood dyscrasia, so one of the tetracycline group of drugs has usually been employed in a dosage varying between 0 25 g and 3 g per day [9-16] But, despite encouraging results in the way of reduced sputum and fewer disabling exacerbations, chemoprophylaxis has not so far been generally adopted, and two investigations in which the findings were at odds with those of previous studies have reinforced this cautious attitude despite the relative ineffectiveness of penicillin against *H influenzæ* the British Tuberculosis Association [17] found that phenoxymethylpenicillin (624 mg daily) did as well as tetracycline (0 5 g daily) in cutting short exacerbations (though neither drug diminished their frequency), and PRIDIE et al [18] failed to detect any worth-while benefit from the administration either of phenoxymethylpenicillin (500 mg daily) with sulphadimidine (2 g daily) or of oxytetracycline (0 5 g daily)

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[9] Recommendations of the International Commission on Radiological Protection Report of Committee III on Protection Against X rays up to Energies of 3 MeV and Beta and Gamma Rays from Sealed Sources Oxford Pergamon Press 1960 Pp 84 21s

[10] Lancet, 1951 i, 517 ibid 1957 ii 760 ibid 1959 i 312 Moorhead J J J Amer med Ass 1943 121 123 Berman S Moorhead J J in [illegible] ed [illegible], O Glasser New York 195[illegible]

[1] Reid L M Lancet, 1951 i, 275

[2] Mulder, J Acta med scand 1938, 94 98

[3] Mulder J J Path Bact 1940 50, 317 Proc R Soc Med 1956 49, 773 Mulder J Goslings W R O, van der Plas, M C, Cardozo P Acta med scand 1952 143 32

[4] Elmes P C Knox K Fletcher C M Lancet 1953 ii, 903

[5] May, J R ibid p 531 ibid p 899 ibid 1954 ii 839

[6] Allibone E C Allison P R, Zinnemann K Brit med J 1956 i 1457

[7] Brumfitt W Willoughby, M L N Bromley, L L Lancet 1957 ii 1306

[8] Lees A W McNaught W ibid 1959 ii 1112

[9] Helm W H May, J R, Livingstone, J L ibid 1954 ii 630, ibid 1956, i 775

[10] McVay L V Sprunt D H Arch intern med 1953 92 833

[11] Edwards G Buckley, A R Fear E C Williamson G M, Zinnemann K Brit med J 1957 ii 259

[12] Edwards G Fear E C ibid 1958 ii 1010

[13] Moyes E N Kershaw R A Lancet 1957 ii 1187

[14] Buchanan J Buchanan W W Melrose A G McGuinness J B Price A U ibid 1958 ii 719

[15] Moyes E N Kalinowski S Z Tubercle Lond 1959 40 112

[16] Murdoch J McC Leckie W J H Downie, J Swain R H A Gould J C Brit med J 1959 ii 1277

[17] British Tuberculosis Association ibid 1960 i 297

[18] Pridie R B Datta N Massey D G Poole G W Schneeweiss J Stradling P Lancet Oct 1, 1960 p 723

In view of the uncertainty of the place of chemoprophylaxis in the management of chronic bronchitis, a report by NOACH[19] of further experience of tetracycline prophylaxis in a Swiss hospital is welcome. He studied 13 chronic bronchitics all of whom were subject before admission to hospital to frequent episodes of infection. They remained in hospital throughout the period of investigation, and accordingly supervision of progress was close and continuous. Patients were accepted for the trial only if their sputum could first of all be sterilised by the administration of antibiotics in full doses, and the dose of tetracycline required to keep the bronchial tree sterile was then determined by serial bacteriological examinations. In 6 cases 500 mg. daily, and in 5 cases 750 mg. daily, was required; in 2 cases even a dose of 1 g. daily was not enough. In the 11 cases in which effective tetracycline prophylaxis was achieved, infection-free periods of from 140 to 192 days were observed, whereas before admission to hospital the mean infection-free period had varied from 3 to 21 days. After infection-free periods lasting at least ten times longer than the average infection-free period before the start of the trial, six control periods without tetracycline were intercalated in 5 cases: in three of these six control periods the sputum rapidly became infected again. In conformity with previous experience the dominant organisms found in sputum before prophylaxis were *H. influenzæ* and the pneumococcus. *Neisseria catarrhalis* was also rather commonly found, and NOACH considers that it should be regarded as a potential pathogen. During tetracycline prophylaxis bacteria less commonly associated with bronchial infection made their appearance—*Klebsiella pneumoniæ*, proteus, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*—and, although they often disappeared spontaneously without causing symptoms and without altering the character of the sputum, sometimes they produced clinical deterioration, occasionally even when still tetracycline-sensitive.

NOACH concludes that tetracycline chemoprophylaxis may be of great value to the chronic bronchitic with frequent exacerbations of infection, but he emphasises that for the best results it is essential first of all to sterilise the bronchial tree and then to give a high enough maintenance dose of tetracycline to keep it sterile. The macroscopic appearance of sputum, he believes, is not a sufficiently accurate guide as to whether infection is present or not: careful bacteriological control cannot be dispensed with. Although he does not deny that tetracycline chemoprophylaxis may still be of benefit even in cases where the sputum has not been sterilised, he points out that there is a risk of the patient finishing up with a bronchial flora resistant to tetracycline and perhaps to all available antibiotics. He does not favour the immediate and automatic treatment of infective episodes with 1 g. tetracycline for 5 to 7 days, since he believes that this dosage may fail to eradicate bronchial infection completely.

Nevertheless, good results have been claimed for this method,[19 20 21] and, since with it supervision is relatively easy, it seems worth further trial in bronchitics whose respiratory tracts are not chronically infected. For patients seriously disabled by infection, continuous prophylaxis seems clearly preferable, and this is a more onerous undertaking. While the balance of evidence suggests that it may have a valuable place in the management of chronic bronchitis, more knowledge is needed about the type of case for which it is appropriate and about the conditions which determine success or failure. It should be unnecessary to justify effective prophylaxis on economic grounds, but, all things considered, it is not expensive.[19 22] Ineffective prophylaxis, on the other hand, is not only costly: it is potentially dangerous to the patient and to others as it may produce a drug-resistant bronchial flora. Thus, until further information is forthcoming, continuous chemoprophylaxis should perhaps be undertaken only where progress can be fully checked and the results analysed.

Annotations

GHANA AND LIVERPOOL

IN Ghana the National Research Council has decided to establish an Institute of Tropical Medicine and Endemic Diseases, to be developed in close association with the Liverpool School of Tropical Medicine. Formed in consultation with Prof. B. G. Maegraith, dean of the school, the scheme was instigated by the President of Ghana, Dr. Kwame Nkrumah, who has taken a great interest in it since its inception.

The institute will give courses of training to Ghanaian and expatriate medical graduates who have been trained abroad and intend to practise in Ghana. Until there is an undergraduate medical school in Ghana, most doctors who work in that country are likely to have been trained largely in curative medicine as practised in Europe and America—without the emphasis on the social and preventive side of community-wide disease that is necessary for practice in rural tropical areas. The courses given by the staff of the new institute will be designed to meet this rather different need, and perhaps at some later stage the teaching now to be evolved will prove useful in constructing an undergraduate curriculum. At the same time research on aspects of the local diseases, and on the vital statistics of the country, will be undertaken with the immediate object of improving health. Here the work of the institute will be complementary to that of the existing medical and other services, including the university.

In these developments the Liverpool school will actively assist—e.g., in the recruitment of expatriates and of Ghanaians. Full details have not yet been worked out, but there will be close liaison between institute and school with regard to teaching and research. For instance the school will from time to time second members of its staff for short-term projects, including lecturing and research, and later some exchange of staff is likely. Also the school has agreed to take Ghanaian postgraduates for training in research, teaching, hygiene, and so on, and Ghanaian technicians will be trained in the school On the other side, housing and laboratory space are to be provided in Ghana for members of the staff of the school who have been seconded to work there

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[19] Noach, A. S. Inaugural dissertation for the degree of doctor of medicine, University of Zurich. Amsterdam: H. J. Paris, 1960.

[20] Elmes, P. C., Fletcher, C. M., Dutton, A. A. C. *Brit. med. J.* 1957, i, 1272.

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[22] May, J. R., Oswald, N. C. *ibid.* 1956, ii, 814.

SIMPLE ULCERATION AND CANCER

THE skin provides ample evidence of the tendency of inflammatory or ulcerative lesions to become malignant examples are lupus vulgaris, chronic leg ulcers, and old scars from other causes This tendency may prove to be an important factor in the understanding of malignant disease, and any evidence indicating universality of this trend would clearly be of value Such evidence has been forthcoming from observations on the alimentary tract Here long-continued chronic inflammation may manifest itself in gastric or duodenal ulceration, regional enteritis, or ulcerative colitis There is growing evidence that the colon has the same malignant potentialities as skin, since it is now being accepted that the incidence of malignancy is increased by ulcerative colitis [1], that the persistence of inflammatory changes is an important contributory factor, since this incidence rises with the duration of the disease, and that, as in the skin, longstanding scars are as dangerous as persistent ulceration since not infrequently cancer develops in cases which have become quiescent [2] That no evidence has been forthcoming regarding regional ileitis is almost certainly due to the relatively recent recognition of this disorder, with rather less than thirty years of clinical observation, malignancy would only now begin to be identified as a sequel Crohn [3] himself reported cancer in only 1 of 676 cases, the case not being recorded in any detail But since 1955, when Hughes [4] first noted malignancy in a case of regional jejunitis, 5 further instances have been reported, and now Buchanan et al [5] have reported a further instance, and Zisk et al [6] 2 instances—though in 1 of these it is not clear whether malignancy followed or coincided with regional ileitis In general it is epithelium that is apparently susceptible, but Hughes' case was of reticulum-cell sarcoma, possibly mesothelium is subject to the same law of malignant change but, being less at risk since it is more seldom damaged by inflammation, malignant change in it is less common There still remains one great anomaly why does persistent duodenal ulceration not give rise to cancer?

PRISONS IN WILD PLACES

Dartmoor Prison was started in 1806 to hold French prisoners-of-war, and it did not receive convicts until 1850 In its earliest days it was described as "a great tomb of the living" [7] Since then it has been much rebuilt but not greatly improved The fabric of the building has latterly needed more and more attention the perimeter wall crumbles intermittently away, nor are some of the staff quarters in much better shape For these and less material reasons, the Home Secretary's recent decision [8] to move the prison to another site has been widely welcomed Prison officers and their families dislike the life in that remote and gloomy place, and, from very different motives, the National Parks Commission and the Dartmoor Preservation Association will gladly speed the parting prison Mr Butler's decision was made despite the committee of inquiry's recommendation that the Prison Commission should be allowed to erect a new prison near the old

The chief difficulty arising from the Home Secretary's decision is its effect on the Princetown community which depends for its livelihood largely on the prison and the visitors it attracts Though the evacuation will be protracted, Princetown may ultimately become a "ghost town" Economic development of the Moor has proved persistently frustrating extensive afforestation and cattle-raising would be unlikely to bring relief to this furthest point from larger centres

The move accords well with the present trend in prison care and is undoubtedly wise Adequate staffing plus modern methods make the security of a remote site less significant Nearness of industry and ease of access to relatives are essential to current ideas about rehabilitation, and day-to-day administration will be much easier Nor has the gaunt environment of the Moor helped much in reforming the persistent offenders sent there, despite the impressive changes in communal atmosphere wrought by the last two governors The Alcatraz approach in the care of the mentally and socially ill has fortunately lost its place in psychiatry and penology

MEDICINE IN THE FACTORY

A VAST number of premises lie within the province of the factory inspectorate—over 220,000 factories, 50,000 building operations, and thousands of docks, warehouses, and works of engineering construction The larger organisations have set up their own health services, which have proved successful in the eyes of employers and employees alike But in 97 7% of industrial premises fewer than 251 people are employed half the total labour force, subject to inspection, work in these small units Last year, commenting on Lord Taylor's account of the joint industrial health service at Harlow,[1] we argued that the industrial health service of the future might be mainly *clinical* and should be divorced from the duties of enforcement carried out by the inspectorate, and that the smaller enterprises should combine, as at Harlow and at Slough, to provide such a service [2] There is much, we think, in Lord Taylor's view that preventive medicine develops most naturally out of curative medicine—that both workers and management listen most readily to the doctor who has won their confidence as a clinician Another attraction of this scheme is that, being unofficial, it is feasible without controversial legislation and that progress could therefore be made at once

Meanwhile, as its new report [3] shows, the factory inspectorate is undermanned for its statutory duties At the end of the year there were 409 inspectors, with vacancies for a further 30–40, of these only 18 were doctors, and 5 of these were working at headquarters This small staff records, analyses, and classifies accidents that prevent workers from earning a full wage for more

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1 Slaney G Brooke B N *Lancet* 1958 ii 694
2 Svartz N Gillnas T *Amer J dig Dis* 1958 3, 537 Rosenqvist H Ohrling H, Lagercrantz R Edling N *Lancet* 1959, i 906
3 Crohn B Yarnis H Regional Ileitis New York, 1958
4 Hughes R K *Amer Surg* 1955 21 770
5 Buchanan D P Huebner G D [illegible] S C North R L, Novak T D *Amer J Surg* 1959 97 336
6 Zisk J Shore J M Rosoff L Friedman N B *Surgery* 1960 47 970
7 *Howard D L The English Prisons London 1960*
8 *Hansard* House of Commons Dec 1 1960 col 83

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1 Taylor Lord *Lancet* 1959 i 875 933
2 ibid p 923
3 Annual Report of the Chief Inspector of Factories 1959 Cmnd [illegible] H M Stationery Office 1960 [illegible]

than three days (of which there are about 6000 on each working day), enforces those sections of the Factories Acts designed to prevent accidents, and educates those concerned in the causes This is valuable and fruitful work last year the number of fatalities was the lowest ever recorded, though unhappily accidents to young persons rose to 11,001 from 9838 in 1958

The medical inspectors are helped by the appointed factory doctors (2179, mostly employed part-time), and these may indeed be regarded as the principal regular medical field force the factory department possesses From them comes most of the initial notifications of industrial diseases, and they regularly inspect all workers in dangerous processes But they do not, of course, provide the kind of clinical industrial service which Lord Taylor wants to see in each locality, nor do they yet constitute the kind of medical link between the schools and industry which Herford [4] thinks so necessary For reasons which we have discussed,[2] [5] this country still lacks the intelligently planned industrial medical service to which the workers are entitled and for which it could, if need be, find the necessary resources, and we cannot feel that time alone can be relied on to remedy the defects of a system which has never been anything but incomplete

ADRENOCORTICOTROPIN

One of the most intriguing aspects of biogenesis is the curious manner in which the animal organism synthesises the steroid hormones from acetate The anabolic sequence of acetate (C_2), mevalonic acid (C_6), isopentenyl phosphate (C_5), squalene (C_{30}), and cholesterol (C_{27}) is well established, and, despite the complex changes involved, this sequence can be achieved by a variety of somatic cells But only in the endocrine glands, and in the adrenal cortex in particular, can the subsequent changes which lead to the formation of corticosteroids, progestins, androgens, and œstrogens be initiated Basic to the formation of all these hormones is the conversion of cholesterol to pregnenolone (3β-hydroxy-pregn-5-en-20-one)—a step which is promoted and perhaps initiated by the adrenocorticotropic hormone secreted by the pituitary

The synthesis of a polypeptide with the full biological activity of adrenocorticotropin (corticotrophin) has been announced by the team of biochemists at the University of Pittsburgh led by Dr Klaus Hofmann [6] The essential structure of this tropic hormone was defined largely by the work of Bell et al [7] who established the basic structure of α-corticotropin (from sheep) and β-corticotropin (from pigs) as a straight chain of 39 aminoacid residues, the species difference lies in a slight alteration of the aminoacid sequence This group also established that the terminal 11 aminoacid residues were not essential for biological activity, and the successful synthesis by Hofmann of a 23-aminoacid polypeptide with full activity indicates that a further five residues are unnecessary Two peptides—α and β melanocyte-stimulating hormones—which stimulate the pigment cells and so darken the skin of cold-blooded vertebrates, have been known for some time to be terminal fragments of the adrenocorticotropin molecule, and incidentally to the main work the Pittsburgh team have synthesised a polypeptide of 13 aminoacid residues with full melanocyte activity

The synthetic adrenocorticotropin is claimed to represent the largest protein-like molecule yet synthesised This is indeed a remarkable and important development, but synthetic adrenocorticotropic hormone is unlikely to supplant, at least in the near future, preparations obtained from animals sources, which are eminently satisfactory in clinical practice There is hope that the pure hormone will aid study of the mechanism by which the tropic hormone acts at its target organ

URINARY INFECTION IN THE YOUNG

The dangers of chronic pyelonephritis and the problems associated with its treatment have been increasingly recognised of late years Often insidious in its onset, the condition may escape recognition until irreversible renal damage has occurred, at which stage antimicrobial therapy is of limited value The early detection of urinary infection, especially in children, may thus be especially rewarding

In a survey in a small township in Virginia, Kunin et al [1] applied screening-tests for urinary infection to 3057 young people aged 5–20 Clean-voided specimens from each sex were subjected to routine laboratory investigation, including tests for bacteriuria From these studies it appeared that a colony count of over 100,000 per ml was a useful criterion of infection Comparison with specimens subsequently obtained by catheterisation from the girls in this group showed that lower counts were of little significance, whereas 43% of those with over 100,000 colonies in the clean-avoided urine had similar high counts in the catheter specimens In this way 15 girls (1%) were found to have significant bacteriuria, but no infections were encountered in 1647 boys In 13 of the girls in whom infection was detected urinary disease had not previously been diagnosed, and no pus was detected in their urine at the initial examination, but further investigation revealed significant pyuria in 5 Among the 15 girls with significant bacteriuria, excretion urography revealed reduplication of the renal pelvis in 2, nephroptosis in 1, and hydronephrosis and hydroureter in another Cystograms in 13 of the girls showed vesicoureteral reflux in 2, possible reflux in 2, and a trabeculated bladder with suspected bladder-neck obstruction in 1 There was no definite correspondence, however, between the detection of such abnormalities and the ultimate recognition of pyuria

While these findings may be of considerable epidemiological interest it is questionable how far such surveys should be extended Although a large measure of parental cooperation was obtained in the community in which the survey was carried out, it is debatable whether this would always be forthcoming elsewhere The importance of detecting 1% of cases with bacteriuria and an even smaller proportion with anomalies of somewhat doubtful clinical significance has to be balanced not only against the psychological disadvantages of such an investigation but also against its inconvenience and possible risks The survey is, however, welcome as a guide to the pattern of urinary infection in young people

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Sir Howard Florey has been elected president of the Royal Society in succession to Sir Cyril Hinshelwood ment of the patients Harmony of purpose, not always linked with diagnostic agreement, has led to a useful exchange of experience at all levels of seniority, and between the specialties of psychiatry and neurology

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[4] Herford M E M Youth at Work London 1957 See *Lancet* 1957, i 1026

[5] *Lancet* 1952 i, 142

[6] *N Y Times* Dec 3, 1960

[7] *J Amer chem Soc* 1956 78 5051, 5059, 5067

[1] Kunin C M, Southall, I, Paquin A J *New Engl J Med* 1960, 262, 817

Observation-unit practice provides excellent teaching material for both undergraduate and postgraduate students, and can be valuable in training for higher examinations—not only in psychiatry There can be few groups of patients so likely to sharpen the wits of the clinician As Asher (1956) says " I have found the work a clinically rich and mentally stimulating addition to my general medical work which I would be loth to relinquish "

It is impossible to provide the best service for the patients without access to a full range of diagnostic facilities and investigations, and especially, for the cases under consideration, to skilled radiology, electroencephalography, and clinical pathology Immediate surgical and general medical facilities are also essential, the most important perhaps being the assistance of a neurosurgeon

In planning for future neurological and psychiatric services for the country in general, it may be worth considering the possibility of creating regional centres sited in such a way as to serve the combined neurological, neurosurgical, and psychiatric needs of a population group, and to be closely linked with a large general hospital We consider that such units would be far more economical and productive of improved results than the use of non-integrated specialist appointments, without adequate ancillary services

We are sincerely grateful to members of the Association of British Neurologists for much helpful discussion

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RADIOLOGICAL HAZARDS TO PATIENTS

Recommendations of Adrian Committee

THE report discussed in a leading article on an earlier page is the work of a committee* appointed in 1956 " to review the present practice in diagnostic radiology and the use of radiotherapy in non-malignant conditions and to make recommendations " Their proposals for reducing the dose of radiation involved in diagnostic radiology and radiotherapy include the following

General

There should be clear-cut clinical indications before any X-ray examination is undertaken, and it should be ascertained whether there has been any previous radiological examination which would make further examination unnecessary For this purpose the case sheet should have a section labelled " previous X-rays "

To reduce unnecessary examinations, arrangements should be made for the ready availability of previous films and for the routine transfer of films from one hospital to another

All requests for examinations should state precisely the clinical indications and the information required

There should be consultation between clinician and radiologist before extensive or repeated radiological examinations of young individuals are undertaken It must be realised that radiological exposure is just as much the responsibility of the clinician as of the radiologist

To reduce the necessity for repeat investigation strict attention should be paid to adequate preparation of the patient before abdominal investigation

Special precautions should be adopted in the radiography of pregnant women Only essential examinations should be carried out during pregnancy, and particular care should b taken to avoid irradiation of the fœtus whenever possible In all women of childbearing age the clinician requesting the examination should never overlook the possibility of early pregnancy

Any previous history of radiotherapy should be ascertained before a new course of treatment is undertaken Permanent records of all radiotherapy should be maintained and be readily available for transfer from one hospital to another

Consideration should always be given to alternative methods of treatment before radiotherapy for non-malignant conditions is undertaken

Techniques

In every radiological examination, care should be taken to reduce to a minimum the irradiation of the gonads The steps necessary to this end are discussed throughout the report In particular, strict attention should be paid to the following

General to all Forms of Radiology

Limitation of field size —Strict limitation of field size to the area necessary for the particular examination or treatment should be routinely practised In diagnostic radiology, this should be done by fitting light-beam diaphragms rather than circular cones, particularly when a large field size is used

Beam direction —Whenever possible, the beam should not be directed towards the gonads and this should be borne in mind particularly in examinations or treatments of the limbs, especially of the hand with the patient in the sitting position

Gonad shields —Adequate gonad shields should invariably be used in examinations or treatments which are likely to give a high gonad dose, unless they interfere with the proposed examination or treatment

Immobilising devices —In the examination or treatment of children or patients who need support, mechanical devices to ensure immobilisation should be used

Particular to Radiography

High speed films and screens —The use of the fastest films and screens consistent with satisfactory diagnostic value is strongly recommended

Automatic timing devices —Repeat exposures should be kept to a minimum by the use of photoelectric timers or similar devices Where these are not practicable, accurately pre set timing devices should be readily available

Particular to Fluoroscopy

Limitation of use —Fluoroscopy should not be undertaken if the same information can be obtained by radiography It should not b used for locating metallic foreign bodies at operations as electro metal locating equipment is now available

Dark adaptation —No fluoroscopic examination should be undertaken without adequate dark adaptation on the part of the clinician undertaking the examination (at least 10 minutes)

Automatic switches —All fluoroscopy machines should be fitted with a clock, or other timing device which automatically cuts off the beam after a certain time or a certain dose

Image intensification —More general use should be made of image intensification in such examinations as cardiac catheterisation There is urgent need for more research into the problems of image intensification for medical purposes

Particular to Mass Miniature Radiography

In accordance with the recommendations of the committee's report, chest examinations of pregnant women should not be ca

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* The members of the committee were Lord ADRIAN, O M, F R S, F R C P (chairman) Dr L G BLAIR, Prof J C MCCLURE BROWNE F R C S, Lord EVANS F R C P, Mr R J G GREWCOCK, L D S Prof A BRADFORD HILL, F R S Prof R J KELLAR, F R C O G, Dr PETER KERLEY, Dr D R MAITLAND, Prof W V MAYNEORD, D SC Prof J S MITCHELL, F R S, F R C P, Mr C NAUGHTON MORGAN F R C S Dr KENNETH ROBSON, Mr T HOLMES SELLORS F R C S Dr G R SEWARD, Prof F W SPIERS, D SC, Prof L J WAYNE F R C P, Prof CHARLES A WELLS F R C S, and Prof B W WINDEYER, F R C S Secretaries Dr A CRUICKSHANK Mr I H BRANDES and Mr R L BRIGGS

The physics surveys and the translation of the results into material for the committee were organised by Mr S B OSBORN and Mr K E ELLIS, under the general direction of Professor Spiers out with mass miniature techniques, but by full-size films with strict limitation of field size For the chest radiography of children and adults of short stature either technique may be used, so long as adequate steps can be taken to exclude the gonads from the X-ray beam, otherwise large films should be used

Particular to Radiotherapy

In the treatment of skin conditions, use should always be made of the softest quality of radiation consistent with adequate irradiation of the tissues to be treated

Radiation should not be applied to the ovaries for the production of a temporary artificial menopause, or for the treatment of infertility

Equipment

Checks should be made regularly to ensure that all radiological equipment is maintained to the standard laid down in the Code of Practice for the Protection of Persons Exposed to Ionizing Radiations Obsolete and erratic equipment should be replaced immediately The development of automatic devices, and particularly those which reduce the risks of human error, should be actively encouraged

Staff and Training

Attention should be given to the provision at all times of adequate medical and technical staff in radiological departments In sparsely populated areas where radiologists or radiographers are not available, training in the safe use of equipment should be given to the general practitioners or nurses who have to carry out any minor X-ray examinations Adequate instruction should be given in the medical and dental undergraduate curricula on the uses and hazards of ionising radiations

Surveillance

The genetic dose to the population from diagnostic and therapeutic radiology should be kept under effective review by the Health Departments

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Medical Education

THE TEACHING HOSPITAL

FOR the subject of its third annual conference, held in London on Dec 2, the Association for the Study of Medical Education (ASME) chose the Function and Structure of the Teaching Hospital Among the guests were some well-known architects and hospital administrators Sir ROBERT PLATT F R C P, took the chair We refer briefly below to some of the contributions

Sir RUSSELL BRAIN held that in the teaching hospital priority must always be given to teaching, and this principle was now easier to implement since the National Health Service had made special forms of treatment, previously restricted to teaching hospitals, more widely available Research was one of the most important functions of the undergraduate teaching hospital its stimulant effect was felt throughout the hospital, and apart from this " specific metabolic action ", it had the creative function of awakening interest in those who might make a career in medical research Part-time consultants should be given more opportunities to do research, and more whole-time research units were needed In the matter of hospital staffing, was the work of senior registrars always determined by training considerations and not by the convenience of the hospitals concerned? The demand for help for overseas graduates was increasing, and Sir Russell restated his plea for an organisation to arrange the exchange of doctors at senior-registrar level

Prof W MELVILLE ARNOTT saw among the objectives of the teaching hospital the induction of scientifically straight thinking, a keen intolerance of the slipshod, and " a high sense of ignorance " The main educational instrument was example, and apprenticeship was still at the core of the medical-school ethos This country was in the opening phases of a big programme of hospital reconstruction (partly designed to replace those hospitals which had become, in Professor Arnott's phrase, " like the Pyramids, timeless mysteries of masonry "), and the building of teaching hospitals should be a joint hospital-university enterprise, unimpeded by argument about who pays for what share The emphasis in design was shifting away from bed numbers towards laboratory facilities, and this would devalue the prestige of bed numbers, which often became, like car horsepower, a social-status symbol

The ideal to aim at was, in Prof B W WINDEYER's view, the happy state when it was impossible to say where medical school ended and hospital began, and to achieve this it was important to break down barriers between clinical and preclinical staff Research by part-time consultants still needed helping and nurturing Accommodation for research and teaching should be placed near the ward ('one step away is one step too many'), but with this Prof G A G MITCHELL disagreed ('you can't imbed research in the wards "), thus illustrating Professor Windeyer's final point that there was always room for individuality and differences of approach

Discussing the needs of the student, Dr J D SPILLANE recalled how often he had heard it said that today's student was a less cultivated fellow than his predecessor What could we expect when specialisation began at 16? To acquire the two kinds of knowledge he needed—of diseases and of people—he must have the proper environment and that was best provided by a university A gymnasium and a swimming-pool could be just as important as a lecture-theatre The look of the place determined standards, and squalid surgeries often reflected the squalor of the student's first professional environment Dr Spillane's coloured pictures showed some spectacular American developments in teaching-hospital design (at Seattle, Gainesville, and Stanford), contrasted with some more static structures nearer home

Prof CLIFFORD WILSON's first requirement was a staffing system that allowed more time for teaching, that would make it easier to obey the General Medical Council's exhortation, " Educate more and instruct less " In fact he had detected a general reduction in contacts between student and teacher, and certainly research at all levels in teaching hospitals was less than it might have been He also wanted to see the student given access to clinical material in which the acute and common conditions were not overshadowed And it should be generally recognised that the administrative organisation for teaching should be no less important than for other hospital activities

In Britain, Mr D H PATEY remarked, we had two big advantages in our teaching hospitals the tradition that teaching was a privilege as well as a duty, and the acceptance by the public of teaching in hospitals The student should be recognised as an integral part of the medical team, and the title " student doctor " had its merits

Dr DAVID STAFFORD-CLARK said it was invaluable for clinical students to see teachers in action as clinicians, conferring over cases and discussing lines of action But the final answer, according to Prof A. L BANKS, was one of which he had just been reminded by the late Sir Robert Hutchison, whose portrait looked down on the meeting—and that was to provide teachers who could teach But the chairman ruled that there were still good reasons for discussing other provisions

So Prof C H STUART-HARRIS and Dr J D N NABARRO went on to discuss research in teaching hospitals Both agreed on the merits of the critical research outlook as a stimulus to thought, and Dr Nabarro pictured the part-time consultant as a valuable link between wards and research departments At ASME's first conference doubts were raised about the wisdom of introducing the undergraduate to research projects so early in his career, but last week no-one dissented

Sir GEORGE PICKERING was disappointed by the declining use of laboratory methods by clinical students The dust was settling and the ward laboratory was becoming extinct Such inquiries by the student himself were a valuable exercise in integration, encouraging him to view the patient as a whole

In its relationship to the community, the teaching hospital was, Prof THOMAS MCKEOWN believed, *deficient in its service* to the chronic sick and the mentally ill. He wanted to see a closer link between the hospital and the community services. No service could be effective without continuity between home and hospital bed. As things were, a large part of medicine's problems was removed from the teaching hospitals, and this put serious limitations on research. Prof A C DORNHORST would not have it that the teaching hospital should be a microcosm of the medical services as a whole. Patients with chronic diseases should not occupy teaching beds after the medical decisions had been taken. The "wicked uncle" picture of the teaching hospital, taking only patients with large lumps, was surely thirty years out of date.

Among the architects' views, that of Mr ALEXANDER GRAY was that the *whole process of building hospitals was hampered* because people would not make up their minds what they wanted. And he had stern things to say about the delays of *waiting for Treasury approval*.

Dr J H LINDELL, of Melbourne, described progress towards new universities with medical schools and hospitals in Melbourne and Sydney. If more than two doctors were delegated to deal with the architect, the results, in his experience, were bad. What he had seen of hospitals in this country made him marvel at the quality of the work done under appalling conditions.

Sir ARTHUR STEPHENSON, the distinguished Australian architect, declared that the university hospital should undoubtedly be part of the university campus. The basis of successful design was the ward plan and an appreciation of modern equipment. Decentralisation of nursing services was the key to labour-saving. In the matter of costs, much trouble was caused by "guess estimates" and unfair comparison of costs per bed between one building and another.

Conference

WILSON'S DISEASE

FROM A CORRESPONDENT

IT *might at first seem strange that a condition as rare* as Wilson's disease should merit the dignity of an international meeting. Such, however, has been the volume of work on this subject in the past fifteen years that the time appeared ripe to gather together in London scientists from different disciplines to discuss recent advances and to formulate the more important problems for future research. Appropriately the conference, on Sept 20–22, was held at the National Hospital, Queen Square, Wilson's own hospital, and it is hoped that the proceedings will be published in 1961, almost fifty years after the appearance of Wilson's great monograph.[1]

Copper Metabolism

I H SCHEINBERG observed that copper deficiency has been reported in several species, the best example being sway-back in sheep, but so far there have been no clearcut reports of its occurrence in man. This he thought *was due to the ubiquity* of copper in the diet, to the relatively small body requirements (around 100 mg. in a man), and to the fact that, unlike iron, there is no major source of loss from the body. Copper, *however, apparently plays an essential part in some metabolic* processes, and apart from its role in utilisation of iron in hæmoglobin formation it is an essential constituent of at least 7 metallo-proteins (of which *cæruloplasmin, liver copper-protein*, and cerebrocuprein were *later discussed at length*).

In animals excess copper in the diet may give rise to both hepatic lesions and hæmolytic crises—an uncommon, though well-recognised, manifestation of Wilson's disease. In man acute copper poisoning almost invariably leads to diarrhœa and vomiting. Chronic copper toxicity Scheinberg believes to be synonymous with Wilson's disease, and he pointed out that in this condition the accumulation of copper in the tissues precedes the development of the lesion, the copper content of the affected organs may exceed the normal by 100-fold, and an adequate "decoppering" regime results *in clinical improvement*. The relationship of this excess tissue copper to the low cæruloplasmin remains obscure but seems to be associated in some way with a defect in the transfer of copper from the liver copper-protein to cæruloplasmin. As a result, copper accumulates in the liver and is eventually released into the plasma in a form available for diffusion into other tissues and for excretion by the kidney. He knew of no good evidence for abnormalities of other copper proteins in Wilson's disease, such as tyrosinase, cytochrome C oxidase, cerebrocuprein, or liver copper-protein.

This last point was elaborated by A G MORELL, who described the isolation and characterisation of liver copper-protein from both normal and Wilson's disease livers. The aminoacid chains of these two proteins are remarkably similar. The main difference between the proteins is that the copper content of protein from the abnormal livers may exceed the normal by 10-fold. If the excess copper is removed from the abnormal protein its absorption spectrum closely resembles the normal. Similarly if copper is added to the normal protein its absorption spectrum closely resembles that of the abnormal protein. No evidence *was found for the existence of a specific protein in the* Wilson's disease livers with an abnormally high affinity for copper.

An interesting parallel finding was reported by HUNTINGTON PORTER for brain copper-proteins. The concentration of cerebrocuprein is not increased in the Wilson's disease brain, and the excess copper is apparently bound to proteins normally copper-free, the inhibitory effect of this abnormal copper on brain enzymes leads to the development of the characteristic neurological lesions.

This conclusion was supported by K REES, whose enzymatic studies have shown how vulnerable are –SH-dependent enzymes, such as isocitric dehydrogenase, to *inhibition by* copper.

Cæruloplasmins

C G HOLMBERG, one of the discoverers of this blue serum protein, cæruloplasmin, pointed out that the 8 copper *atoms* in the molecule appear to be arranged in *functional pairs*, 4 being in the cupric and 4 in the cuprous state. He suggested three possible functions for cæruloplasmin—as a transport protein for copper, as an enzyme whose physiological substrate is unknown, or as a transport protein for substances other than copper, such as active amines which may then be carried on the protein to their site of detoxification, but for the moment there is no evidence which, if any, of these three *is the physiological* role of cæruloplasmin in the body.

L BROMAN discussed the need for a method of separating cæruloplasmin from whole blood which would not alter the physical or chemical characters of the *protein*. This he achieved by chromatography on hydroxyl apatite and diethyl aminoethyl cellulose columns. By this method he found two distinct peaks of oxidase activity in normal human serum, and one of these, on rechromatography, itself gave rise to two distinct peaks.

The relation of the two cæruloplasmins to each other and the factors governing their relative concentrations was discussed by R RICHTERICH, who has shown that their concentrations always rise and fall together, and he concluded *that* one is either a precursor or a degradation product of the other. At birth, however, only one of these proteins is present in the serum, and thus he designated cæruloplasmin *D*. In the first month of extrauterine life cæruloplasmin C appears in the serum, and at the same time the excess hepatic copper, present in fœtal life, is mobilised so that by 3 months the concentrations *of copper in the liver and* cæruloplasmin C in the blood reach adult levels In respect of the liver-copper storage and the low blood-levels of cæruloplasmin C, the fœtus and the patient with Wilson's disease are therefore remarkably similar, and he suggested that a failure to synthesise a peptidase necessary to convert storage cæruloplasmin D into transport cæruloplasmin C might be the genetically determined lesion in Wilson's disease The relation of the storage cæruloplasmin D of Richterich to the liver copper-protein of Morell is not clear, and further work to determine this point seems to be needed

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[1] Wilson, S. A. K. *Brain*, 1911-12, 34, 295.

The enzymatic properties of cæruloplasmin have been investigated by G Curzon, who has shown that ferrous iron is a powerful activator of the enzyme, and he suggested that an oxidation system may exist in which cæruloplasmin oxidises ferrous iron to the ferric state and this in turn oxidises the substrate while itself being reduced back to ferrous iron In vitro such a mechanism appears to be involved in the oxidation of adrenochrome and 5-hydroxy-indoleacetic acid but not 5-hydroxytryptamine

Genetics

A gene frequency in the general population of approximately 1 in 500 was postulated by A G Bearn, who asked whether the disease was in fact a homogeneous genetical entity and whether cæruloplasmin was the primary gene product The answer to this question, he felt, depended on our ability to identify with certainty the heterozygotes, and on the purification and fingerprinting of cæruloplasmin from both the healthy individual and patients with Wilson's disease

Attempts to detect the heterozygotes with radioactive copper (^{64}Cu) were discussed by I Sternlieb, A G Morell, and I H Scheinberg from New York, and S B Osborn and J M Walshe from London The New York group had estimated the rate of incorporation of the isotope into cæruloplasmin at 48 hours, and by this method had classified 29 of 49 close relatives of Wilson's disease patients, but had been left in doubt about the remaining 20 Osborn and Walshe, working within the more stringent limitations on isotope dosage observed in this country, estimated the liver uptake of copper at 24 hours They studied a large family and believe that they could detect the normal and the heterozygote siblings of a patient with Wilson's disease They pointed out that the distribution of the isotope does not correspond to the calculated body pool of the metal in either normals or patients—an observation which suggests active rather than passive concentration of the metal in the liver

A Sass Kortsak also believed that the failure of the Wilson's disease liver to concentrate copper is not related to prior saturation with the metal, nor did he consider there was evidence that the body pool of copper is increased in the heterozygotes He postulated that the defect in Wilson's disease involves not only the ability to incorporate copper into cæruloplasmin but also the mechanism of concentration at the point of incorporation

In describing the work of the Birmingham school J F Soothill suggested that three metabolic lesions existed involving copper, cæruloplasmin, and aminoacid metabolism, any one of which might be present in the heterozygotes independently of the others—a view which was not generally accepted by other delegates

Hepatic Lesions

H Popper and F Schaffner suggested that the histological picture was rather specific in Wilson's disease The characteristic features observed are ballooned glycogen nuclei, clumping of the cellular cytoplasm, and small fat droplets present in a liver otherwise typical of postnecrotic scarring Effectively treated patients show an arrested lesion, and the self-perpetuating role of autoimmune processes is less distinct than in other forms of cirrhosis

These conclusions, based on histological studies, were supported by Sheila Sherlock's clinical observations She described the hepatic lesion in 4 young girls and the response to treatment with penicillamine As a result of this therapy the deposits of copper in the liver diminished or disappeared, and 3 of the patients improved greatly with disappearance of ascites and neurological signs, but in the 4th, despite a good biochemical response, the hepatic lesion progressed to a fatal outcome The great improvement in the hepatic status of 3 of these 4 patients is of particular interest as it has hitherto been suspected that the liver lesion was progressive in this disease, even when the neurological symptoms improved with therapy At the start of treatment one of these girls had a normal concentration of cæruloplasmin but after two years' "decoppering" this had fallen to classical Wilson's disease levels V M Rosenor has also made a similar observation

The problem thus raised was further complicated by a report by J L German from the Rockefeller Institute that, in some of his patients, it has been possible to restore a low cæruloplasmin concentration to normal levels by the administration of large doses of œstrogens This was usually accompanied by a disproportionate rise in the non-cæruloplasmin serum-copper, and by clinical deterioration, although 1 patient benefited significantly

The results of cæruloplasmin substitution in 4 patients described by H Bickel were also disappointing By giving repeated intravenous infusions of the protein he raised the blood-level to normal and succeeded in keeping it there for 3 months in 1 and a year in another case There was no detectable change in the urinary loss of copper or aminoacids, and the downhill course of the illness did not seem to be modified Such treatment, of course, introduces approximately 0 34% copper with the cæruloplasmin, and possibly infusion of the apoenzyme would be of more value to the patient if the technical difficulties in its production could be overcome

Penicillamine

H V Aposhian reported on the toxic action of the L-isomer of penicillamine This is probably due to its ability to form a thiazolidine with pyridoxine and thereby act as a vitamin-B_6 antimetabolite The D-isomer, however, appears to be non-toxic apart from causing occasional sensitivity reactions Acetyl penicillamine, although not able to promote cupriuresis in man, he has found to be very active in protecting rats against mercuric-chloride poisoning, and it should therefore have a place in the therapy of this condition

In man Walshe has found that penicillamine increases copper excretion by rendering it available for excretion at the glomerulus, and at the same time he observed a fall in the plasma-copper level This suggested that copper had been mobilised from cæruloplasmin, and in-vitro studies with serum and purified cæruloplasmin supported this hypothesis He observed that acetyl penicillamine was also active in vitro, although it did not mobilise copper in the intact animal

Finally, clinical reports on the therapeutic activity of penicillamine were made by J Lange from Bonn, J E Boulding from British Columbia, and D W Sumner and H G Garland from Leeds All 6 patients included in these reports derived much clinical benefit, and 1 of Boulding's cases who had had three previous miscarriages was able to carry through a successful pregnancy Lange remarked on the decreasing cupriuretic effect of penicillamine on long-term administration, and speculated as to whether this was due to depletion of the body stores This view was supported by some clearance studies mentioned by Walshe, which showed that, although the total amount of copper excreted per gramme of penicillamine might fall with time, the clearance remained approximately unchanged in one of his patients after a year of continuous treatment This suggested that there was no true resistance to the drug

Conclusion

If no original observations of major importance were made during the conference, much new and useful information was gathered together for the first time Many of the problems seem as remote from solution today as they did when Wilson published his original description of this rare and fascinating disease almost fifty years ago

This conference was sponsored by the Distillers Company (Biochemicals) Ltd

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"Man, in the psycho scroll I read it needed two probation officers to get one yob and his phobia into school, well my phobia must've been the greatest, yea *big*, because for me it took four officers and a truck even on a half-day, that's how sick I was. I mean is it my fault because they didn't give me no shots or sump'n for it? Man, them squares, the way they just *made* me go to school disrupted my ego-integration and traumatised my psyche like crazy. So when my steady chick says, 'Wow! Lamp that set of threads in that bazaar!', well, it was go, man, go. I mean I just had to have into them threads to get integrated, like I told the old girl with the handbag, me, I just rationalise the transference like I dig Elvis or way-out jazz.

"Even so and all, sick and alone as I was I felt no fear when I later see this police doll, me being a mean man with a bicycle-chain, but it seems she had a Black Belt for Judo. 'Babe, man, hark,' I said to her in some haste, 'play it cool, such trauma is bad for my phobia!' but she went right on screwing my arm round like it was being cross-threaded.

"Like I later exclaimed at the Judge, 'I am a very sick yob, Judge, there is a need to appreciate my associated symptoms and tensions in their proper perspective, this psycho stuff, Judge, you should really get *with* it, Daddy-O! Don't you never watch no TV, or read no books?' I request him. But this old square in the TODD-AO-sized toupee—give me my Cherokee anytime—maybe he's repressed at not playing at the Old Bailey this week, he comes right back at me, saying, 'Yea, man, and the books I read say, for offences of this nature, three years!'

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It is bad enough that nowadays so much specialised information is published in the columns of the *B.M.J.* and *The Lancet* for all to see and digest, but it is still worse that the basic specialist textbooks are on the shelves of every hospital library, open to even the most junior resident. One helpful tip for consultants in these difficult days is to acquire the latest edition of the appropriate "bible", on which so much depends, not as an addition to the hospital library, but as a departmental or laboratory bench reference book, and to pass on the superseded edition to the librarian. This will then grace the shelves, with fly-leaf suitably inscribed as "Donated by the kindness of ..." If the superseded edition has in the first place been bought by the hospital, the transaction is rather expensive.

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Letters to the Editor

ON BEING AN OMP

SIR,—I must have shared pleasure with many others in hearing from "O. D. Lea" (Nov. 26, p. 1188) about his experiences as an omp. He did not, however, make it clear that there are omps and omps. One subspecies is the omp who is also a consultant. This hybrid leads an even more peculiar life than the simple omp.

The typical omp, as portrayed correctly by Lea (Omp 72), leads a life necessarily circumscribed. He is a rather reticent type, usually working in twilight and vaguely conscious that *somewhere* there may be gangs of unscrupulous omps. These he feels must exist because of the elaborate regulations which protect him from the temptation of becoming one. Chief among these temptations is that he might be misguided enough to *treat* a patient. The regulations quite clearly imply that an omp should not provide treatment. The omp must learn to accept this, but so far no omp has been able to explain to a patient how either of them benefit from this. No doubt an omp who could explain the reasons for this convincingly would graduate out of the omp class and become a politician or—if really brilliant—an administrator. To be the latter, of course, he would not only be required to explain the advantages to a patient of not receiving treatment, but also show that it was not to the patient's benefit to know what they were.

In his early days the omp might be tempted to explain to the patient that he could be provided with treatment if he paid a fee. The experienced omp will have found that this suggestion is greeted by the patient with very much the same reaction he would adopt if he were asked to read, as part of his sight test, *Lady Chatterley's Lover* instead of the more usual *Robinson Crusoe*. This reaction reminds the omp of the delicate nature of his work and how close he is to being an undesirable omp. Like omp 72, omp 21 has also transgressed the treatment regulation, but logically to do so for one should lead one to do so for all—hence the slippery slope.

The ruling factor in an omp's life is that he is continuously in danger of doing *too much*. This is how it comes about that the consultant who is also an omp leads an interesting double life. At hospital he is always in danger, chiefly owing to pressure of work, of doing too little for the patient. This is the common situation of all conscientious people—but in his life as an omp he is transformed into somebody who must avoid doing too much. The versatility demanded is often exorbitant and the consultant type of omp develops a "split personality." So much so that it is typical of his activities that he *writes letters to himself*.

Such a situation, for instance, in the life of the hybrid omp arises with a patient with an early cataract. The omp-consultant noting that the condition is pathological, correctly, according to his temporary omplike character, refers the patient to the general practitioner who may or may not have realised when he issued the 'green ticket" that his patient either (*a*) was going to see an omp, or (*b*) was going to see this particular omp. A considerable amount of finesse is required in this situation by the omp, but it frequently can be exercised by the following procedure.

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The general practitioner, versed both in the eccentricities of ophthalmologists and the workings of the N.H.S., finds nothing peculiar in these procedures. He might at the worst consider this conduct ompish.

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However, the evidence that the omp-consultant is *really* two people can be corroborated by witnesses. In his capacity as a wicked omp, patients frequently tell the consultant, "I went to the hospital once but the specialist there was so busy that I was told nothing. I would much rather see *you*, doctor."

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This remarkable effect is not obtained by prisms but by suggestion and atmosphere which surpasses the powers of a Canasta, who so far has not been able to convince us he is two people. Our lives as omps are governed by magical inscrutable laws which all sane people such as general practitioners and patients realise are beyond understanding. We omp-consultants, leading a Jekyll-and-Hyde existence, however, are fascinated by our roles and would miss much if the rules were altered and our double lives merged, so that we were the same people in different places and permitted to exercise our skill wherever we happened to be.

London, W.1. PETER A. GARDINER.

BLOOD-CHOLESTEROL AND ASPIRIN

SIR,—The preliminary communication by Dr. Eidlitz (Nov. 19) is very interesting. He shows that aspirin produced a striking fall in blood-cholesterol level in 10 patients with various arteriosclerotic diseases. For many years aspirin has been used in Torquay in the treatment of thromboses. In 1948 I suggested that a salicylate should be useful for coronary thrombosis[1] because of its anticoagulant and pain-relieving properties. In 1949, with the collaboration of a number of general practitioners, I showed evidence of the value of aspirin in the treatment of vascular diseases.[2] It seems that Dr. Eidlitz may add the third leg to the tripod of virtues required of a drug used for this purpose. I believe that nobody knows how it works.

The Flook-like obstinacy of aspirin in holding its own among antirheumatic remedies may be correlated with its anti-thrombotic effect. It seems a far cry from rheumatism to coronary thrombosis, but in the context of temporal arteritis the relationship is not so improbable. What originally impressed me about the effect of aspirin in coronary thromboses was its power to relieve anginal pain, even when other remedies had failed. Some years before cortisone came on the market, when I was using aspirin for temporal arteritis, its effect on the pain was

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1. Gibson, P. C. *Lancet*, 1948, i, 965.
2. Gibson, P. C. *ibid.* 1949, ii, 1172.

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BLOOD-CHOLESTEROL AND ASPIRIN

SIR,—The preliminary communication by Dr Eidlitz (Nov 19) is very interesting. He shows that aspirin produced a striking fall in blood-cholesterol level in 10 patients with various arteriosclerotic diseases. For many years aspirin has been used in Torquay in the treatment of thromboses. In 1948 I suggested that a salicylate should be useful for coronary thrombosis[1] because of its anticoagulant and pain-relieving properties. In 1949 with the collaboration of a number of general practitioners, I showed evidence of the value of aspirin in the treatment of vascular diseases.[2] It seems that Dr Eidlitz may add the third leg to the tripod of virtues required of a drug used for this purpose. I believe that nobody knows how it works.

The Flook-like obstinacy of aspirin in holding its own among antirheumatic remedies may be correlated with its anti-*thrombotic* effect. It seems a far cry from rheumatism to coronary thrombosis, but in the context of temporal arteritis the relationship is not so improbable. What originally impressed me about the effect of aspirin in coronary thromboses was its power to relieve anginal pain, even when other remedies had failed. Some years before cortisone came on the market when I was using aspirin for temporal arteritis, its effect on the pain was equally remarkable Though not so dramatic, it seems of the same order as the effect of the cortical steroids

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[1] Gibson, P C *Lancet*, 1948, i, 965

[2] Gibson, P C *Ibid* 1949, ii, 1172

It may need another William Harvey to reveal the full significance of aspirin's action, but the best way of testing the extent of its usefulness is to use it I would suggest that this is a piece of field research which should be undertaken by the College of General Practitioners, for this part of the problem is a practical one, and the snags of aspirin therapy are best known to general practitioners Such an enterprise would I am sure be rewarding to patients and doctors

Charlbury, Oxfordshire PAUL C GIBSON

"ATHEROLIPID NUMBERS"

SIR,—The letter of Nov 26 by Dr Searcy and his colleagues prompts me to comment that we have also been able to confirm our 1953 observation of an abrupt postmenopausal rise in serum-cholesterol levels

A more recent study [1] of the serum-cholesterol of 213 healthy women between the ages of 20 and 70 has shown that the difference between the mean serum-cholesterol level of women aged 45–49 and that of women aged 50–54 years is at the 1% level of significance Although the results of this study again suggest that the serum-cholesterol levels of women aged 65–69 are lower than those 10 and 15 years younger, it should be pointed out that the mean level is still significantly higher than the mean levels observed in premenopausal women The explanation of this slight fall is not clear, although it is possible, of course, that those women with considerable postmenopausal elevation of serum-cholesterol do not remain healthy until the age of 65 In this respect, it would be interesting to know whether a woman's serum-cholesterol really reaches a postmenopausal peak and then decreases, or whether the apparent fall during the seventh decade results from group studies on a selected population

Department of Cardiology
The Royal Infirmary,
Edinburgh
M F OLIVER

PREMEDICATION WITH ATROPINE BY MOUTH

SIR,—I was interested in the article by Dr Joseph and Dr Vale (Nov 12) Oral administration of atropine to children before tonsillectomy was described by Gusterson,[2] the dose being gr 1/100—1/50 combined with methylphenytol elixir Incidentally, he did not find the antisialiac effect of the atropine satisfactory but got better results from oral hyoscine For tonsillectomy, especially by the guillotine method, an adequate preoperative dose of atropine is, to my mind, of supreme importance—not only to suppress salivation but more particularly to protect the heart by depressing vagal activity An operation in such a site, which is liable to be associated with some hypoxia and where there is the added hazard of accidental aspiration of blood, calls for all the protection we can give the heart

I can recall one case of cardiac arrest on the table after a guillotine tonsillectomy in a five-year-old boy The child had been anæsthetised with open ethylchloride and ether and the operation had been completed uneventfully, but when the child was turned over the side of the table the heart stopped This child had been given gr 1/75 of atropine by mouth and the episode took place very shortly after I had made the change from atropine by injection Admittedly this complication at such a time may have been mere coincidence, but since absorption of drugs from the intestinal tract is notoriously unpredictable it seems wiser to give atropine at all times by injection

Dublin M MURPHY

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1 Oliver M F Boyd G S *Lancet* 1959 ii 690
2 Gusterson F R *Lancet* 1951 i 910

BATHING-WATER

SIR,—Your leading article of Nov 19 puts the problem admirably It is tragic that most of our rivers are contaminated as a result of our endeavours to improve environmental conditions Might not greater public awareness of this fact, by, for instance, the placing of notices on river banks drawing attention to the contamination, eventually lead to swifter action in effecting a general clean-up as suggested by the Society of Medical Officers of Health?

It is surely not right that the public should be denied either the knowledge that they are about to bathe in dilute sewage or the opportunity of making their own decision about the wisdom or otherwise of bathing in such waters

Cambridge
P A TYSER,
County Medical Officer

HÆMODIALYSIS COMBINED WITH ULTRAFILTRATION

SIR,—We were interested in the paper (of Nov 12) by Dr Twiss and Dr Paulssen on hæmodialysis combined with removal of water by ultrafiltration, using the Alwall artificial kidney

Clearly the rate of ultrafiltration must be related to the degree of hæmoconcentration of the blood used for dialysis In-vitro studies such as they report, where the hæmatocrit is not recorded, are difficult to interpret Our experience of ultrafiltration with the Kolff twin-coil artificial kidney indicate that it has a considerable advantage over the Alwall kidney in removing water from the overhydrated patient

In-vitro studies were carried out to establish the relationship between outflow pressure (measured with an aneroid tonometer) and ultrafiltration (measured by weighing the blood reservoir) at a flow rate of 400 ml per minute, which in our experience has been near the optimal rate for removal of urea [1] The hæmatocrit was adjusted to 35% by the addition of physiological saline to banked blood

In a series of patients admitted with oliguria associated with overhydration, the amount of water removed by ultrafiltration was assessed by hourly measurements on a bed-weighing machine

Fig 1 shows that increments in outflow pressure up to

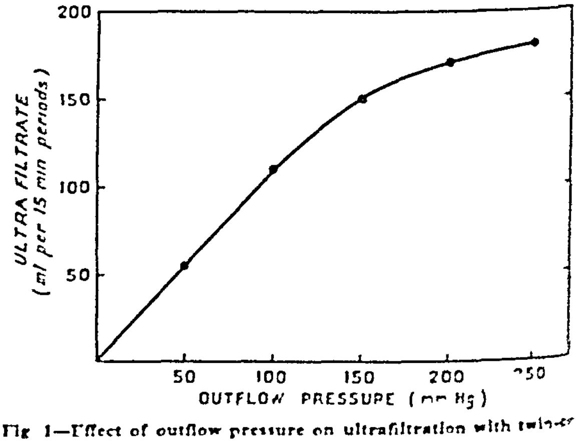

Fig 1—Effect of outflow pressure on ultrafiltration with twin-coil artificial kidney

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1 Kolff W J Watschinger B *J Lab clin Med* 1956, 47, 969

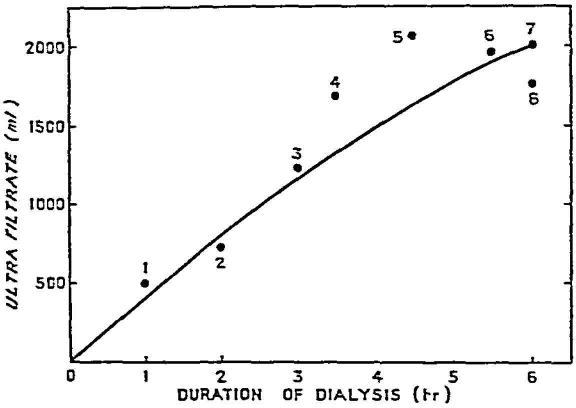

Fig 2—Water removed by ultrafiltration in 8 selected cases

150 mm Hg produce fairly uniform increases in rate of ultrafiltration (up to 600 ml. per hour) Further increments up to 250 mm. Hg do not significantly increase the volume removed. In cases where maximal ultrafiltration was desired, therefore, we have aimed at keeping the outflow pressure at about 150 mm. Hg which is well within the safe range with these coils Fig 2 shows the results in 8 selected cases where dialysis was undertaken partly to correct overhydration All these patients were severely uræmic and had low hæmatocrits It will be seen that up to 2 litres of water were removed in four to six hours Hypotension from over-rapid extraction of water was not observed in any case

Dr Twiss and Dr Paulssen achieved their maximal ultrafiltration (300 ml. per hour) with a flow-rate (10–12 litres per hour) which is lower than their optimal rate for dialysis of urea. This seems to be an inherent disadvantage of their apparatus With the Kolff twin-coil artificial kidney, maximum ultrafiltration is obtained at flow-rates which are optimal for urea and electrolyte exchange.[1]

The London Hospital,
London, E.1

H D Ritchie
G C Lloyd-Thomas
R. H Balme

NEW IDEAS ON EPIDEMIC VIRUS INFECTION

Sir,—In your leading article of Nov 19 you note that Hemmes et al.,[2] working with virus suspension aerosols, find that the survival of poliomyelitis virus and influenza virus are affected by the relative humidity of the atmosphere

> 'In the case of influenza virus (PR8 strain) inactivation of infectivity was slow in the drier conditions and over 10 times more rapid in the moister conditions The reverse held for a strain of poliovirus type 1, which survived well at relative humidities above 50%, but which at 40% or lower was inactivated so quickly that no virus could be recovered from an aerosol 30 seconds after spraying '

I find it difficult to reconcile these laboratory findings with epidemiological studies in the field In Cornwall, epidemics of poliomyelitis have, more often than not, been associated with warm, dry summers

I have plotted the incidence of poliomyelitis in Cornwall 1911–1958 against (1) the average mean temperature for the 3rd quarter (July, August and September), and (2) the average humidity at 9 A.M for the 3rd quarter

The meteorological records used are supplied by the Observatory Committee to the Royal Cornwall Polytechnic Society and the Falmouth Borough Council The observatory is at Falmouth.

In the span of 47 years, notifications of poliomyelitis were exceptionally high (more than 0.1 per 1000 population) on 4 occasions, 1911*, 1947, 1949, and 1950 Exceptionally hot summers in which the average temperature for the 3rd quarter was more than 3° above the 60-year average, occurred in 4 years—1911, 1933, 1947, and 1949

Humidity in Cornwall is high readings around 85% being the rule. I have humidity readings only for the years 1911–1952, but in these 40-odd years humidity in the 3rd quarter was less than 80% on only 8 occasions which include 1911, 1947, and 1949

Thus, in Cornwall between 1911 and 1957 there were 4 major outbreaks of poliomyelitis 3 of which were during summers of exceptional heat and low humidity

The high incidence of 1950 was largely an extension of the epidemic of the previous year many of the 1950 cases coming in the early months of the year

At Greenwich Observatory the average humidity for the 3rd quarter for the first half of the century was 77%

The average temperature and humidity at Greenwich for the 3rd quarter of the years of epidemic paralysis (1911, 1947, 1949) (with the reading of the year immediately preceding) were

Year	*3rd quarter average temperature*	*Departure in degrees from 50-year average*	*3rd quarter humidity (%)*	*Departure from 50-year average*
1910	59.3	−1.2	Not available	
1911	65.7	−5.2	"	"
1946	61.1	−0.6	78%	−1%
1947	65.2	−4.7	70%	−7%
1948	61.0	−0.5	77%	0%
1949	65.5	−5.0	71%	−6%

The findings are the same as in Cornwall—a high average temperature and low humidity associated with epidemic poliomyelitis

July, August, and September are months in which central heating and domestic fires are little in use, consequently, humidity indoors and out are much the same

In this county the inactivities of poliomyelitis virus at humidities of 40% or lower would seem to be of more academic than practical value.

E R Hargreaves,
Deputy County Medical Officer,
Cornwall County Council.

Mawnan,
Near Falmouth.

IS RADIOLOGICAL EXAMINATION OF THE ANKLE REALLY NECESSARY?

Sir,—I certainly agree with Dr Garfield (Nov 26) that a very large proportion of sprained ankles can be treated without X-ray examination I regret, however, that I cannot agree with the arguments he puts forward for his conclusion.

In my department we have made a special study of the ankle since 1953 and since that time we have seen over 1000 cases per year In 1954 we saw 1205 cases, of which 800 showed no bony injury, and of the remaining 400 about 200 showed trivial avulsion of bony fragments By charting the area of swelling and tenderness, we have come to recognise certain types of lesion in which we can be clinically certain that there will be no fracture. The commonest type is that in which there is a swelling stretching from the tip of the lateral malleolus about $2^1/_2$ fingers' breadth above. This swelling extends in front of the malleolus but in the first 24 hours does not spread significantly behind the malleolus This swelling usually occurs very quickly indeed after the injury The shape of the swelling and the fact that it appears so quickly are to us certain evidence that no fracture is present. I rarely X-ray these cases My house-surgeons after a few weeks' experience in seeing these cases also rarely X-ray them, for they have learnt that no fracture is ever seen

Careful charting also segregates another type of swelling associated with inversion strain of the ankle In this, the swelling is below and in front of the lateral malleolus If this case is X-rayed, it may show in a proportion of cases, avulsion of a flake of bone from the talus or navicular bones As the treatment will be exactly the same with or without avulsion of the flake of bone, there is certainly no object served in X-raying this type of lesion

Tenderness confined to the base of the fifth metatarsal

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2. Hemmes, J H., Winkler K. C., Kool S M. *Nature Lond* 1960 188 430

* From report of Local Government Board.

is not a sure indication of fracture, but I will admit that in three cases out of four a fracture is present The lesion is caused by attempted avulsion of the perineus brevis and/or tertius from its point of insertion in the base of the fifth metatarsal Sometimes bone is avulsed with the tendon leading to fracture As the length of treatment for a fracture as opposed to a simple partial avulsion of the tendon tends to be two to three weeks longer, an X-ray is useful here as an aid to prognosis I agree that this is not really necessary, for treatment is continued until tenderness disappears

In all these types of lesion after a twist of the ankle, X-ray examination is not necessary as an aid to treatment In our experience, when there is swelling over both malleoli, a fracture is likely, and it is our rule that all such cases must be X-rayed If the case is seen within the first 24 hours (as described by Dr Garfield) bruising is commonly absent It has been my experience, however, that after 24 hours bruising is present in 9 out of 10 cases After 24 hours, as a general rule, the absence of bruising suggests a quicker period of healing, but this is not a universal rule

It is very gratifying, however, to find in another hospital that X-rays are regarded as a procedure to assist treatment and not just as a rigid necessity

Casualty Department,
The General Infirmary at Leeds

M ELLIS

SIR,—Dr Garfield's article stimulates me to reply that, providing the patient's history, clinical condition, and future possibilities are considered with all humility by the surgeon, the answer to this question is emphatically No

I have recorded the best results of the most serious injuries where no radiographs were taken, and I have seen the worst results when the radiographs have been misinterpreted, and the patient's clinical condition and the possibility of damage by activity have been insufficiently considered I have published case-histories with results in my book and more recently in a paper, Roentgenograms their true value to the surgeon [1] These illustrate that panic, as expressed by Wilfred Trotter, or incompetence must never be allowed to dominate treatment and that the best results are when " *we make no haste in time* of trouble " I have repeatedly stressed that " the *good* radiograph spares the patient pain when judged by competent men, whereas any radiograph which incites the infliction of unnecessary mental or physical pain is a *bad* radiograph " This in no way refers to the so-called quality of the radiographs

Birmingham

JAMES F BRAILSFORD

SIR,—Interested as I was in Mr Garfield's article, I feel I must disagree with his conclusion that the absence of any swelling is a firm indication of the absence of any significant bony or ligamentous damage, whatever the circumstances of injury

This may be true if one sees the patient several hours after injury, but it is certainly not a reliable indication if one sees him immediately after the injury My experience has taught me otherwise

Vauxhall Motors Ltd
Luton

A J DE KRETSER

A MASSIVE OVARIAN CYST

SIR,—May I enter Mr Foreman's competition (Nov 26) for outsizes in ovarian cysts? I cannot approach his Olympic record, but should like him to know of a patient upon whom I operated in 1949

A Chinese slave girl under 5 feet in height and aged 22 arrived at my hospital after an exciting escape from slavery in one of the mountain recesses in China She was brought by her betrothed husband, and because of the size of her abdomen she could only stand with the support of a long stick to prop her Before operation her weight was 141 lb and a week after she was 69 lb, so the tumour weighed about 72 lb The incision from xiphisternum to symphysis pubis showed that there was no trace of any line of cleavage between peritoneum and cyst wall In view of her condition I decided to marsupialise the cyst After opening the cyst and swabbing dry the theatre floor, the abdomen appeared completely empty and no viscera could be recognised or palpated through the thick, spongy cyst wall This was sewn to the whole length of the abdominal wall and the cavity packed with all the sterile linen available After 3 months the cyst had shrunk to a pocket which comfortably took one hand inserted through a letter-box type of opening It was dry and she found it a safe place to keep her few trinkets No skin had been excised and by this time the grotesquely deformed chest and huge folds of abdominal wall had regained their normal contours Two months later the shallow depression, oval and 4 in in long diameter, was closed by suture after excising the remaining piece of cyst wall

The girl, who had been wizened, wrinkled, and quite bald on admission, regained a full head of hair and her youthful appearance and left hospital where her husband had been given a job while waiting for his wife

Eastry, Kent

J R ROSE

HYALINE MEMBRANE FOLLOWING TOTAL BODY RADIATION

SIR,—The letter of Captain King and his colleagues (Dec 3) adds little to their first communication

It is not possible by total body irradiation to give a cancerocidal dose The question is whether the total body irradiation of people dying from recurrent, and now disseminated, cancer deserves the name of therapy At almost any dose the result can only be to increase misery and accelerate death, whatever the efforts at resuscitation

The dose given remains unspecified It was sufficient to produce, in patients who survived their " therapy " by two weeks, the pathological condition of the lungs in which the authors are interested

To investigate this condition in dogs they gave between 600r and 1000r These are lethal doses

Manchester

J L DOBBIE

NICOTINIC ACID IN ISCHÆMIC DISEASE

SIR,—Dr Goldsborough (Nov 12) writes that the two bus-drivers who were allowed to resume driving after a coronary thrombosis are " seen and examined twice a quarter " Such frequent examination suggests that there is some anxiety about a recurrence which, if it happened at the wheel, could cost many lives But examination, however frequent, does not prevent a recurrence Also, Morris et al [1] have shown that men who have had a coronary thrombosis may be as much as ten times more likely to have a second attack than men who have never had one are to have their first The only safe rule with drivers of public-service vehicles is to take them off driving duties when they have shown definite evidence of coronary-artery disease They drive a heavy vehicle which is presumably capable of greater damage than a smaller one, through streets which are commonly crowded, in addition these drivers have responsibility for the safety of passengers It does not follow that all patients who have had a coronary thrombosis should be forbidden to drive a car

The real question is " What degree of risk is acceptable? ", and we are at present groping our way towards an answer We need to know how many accidents annually result from coronary thrombosis in car-drivers before we can consider this question adequately I suspect there are not many, but most chief constables can quote an accident in which several people were killed, and after which a driver was found to have had a coronary thrombosis. This is probably a level of risk in life which must be faced and accepted, but bus-drivers have a special responsibility and should not drive after they have shown definite evidence of coronary-artery disease.

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[1] J int Coll Surg 1960 34 257

[1] Morris, J N, Heady J A, Barley R G Brit Heart J 1957 19 [illegible]

London Transport Executive,
London N W 1

L G NORMAN

HYPERSENSITIVITY TO MILK AND SUDDEN DEATH IN INFANCY

SIR,—The possibility that cow's milk proteins in the air passages of sensitised infants can cause anaphylactic shock leading to death (Nov 19) is of immense interest to evaporated milk manufacturers. The interest arises from two of the major advantages claimed for this type of milk.

(1) The fine soft curd derived from the casein content. Tolerance of this curd has been demonstrated in normal and difficult infant feeding over the past thirty years, and opinions suggest that regurgitation of evaporated milk is extremely unlikely. Thus, if shock be due to aspiration of regurgitated food from the stomach, wider use of evaporated milk could lead to some reduction in deaths in infants from this cause.

(2) The proteins of evaporated milk which have generally been regarded as less likely to cause allergic reaction, because of

(*a*) The triple heat treatments peculiar to evaporated-milk processing.

(*b*) The very substantial physical pressure (in excess of 1 ton per sq in) used to homogenise butterfat, and which also exerts influence on the proteins. There is evidence that the whey proteins of evaporated milk undergo changes during these processes and become more suitable for use in, say, the eczema asthma syndrome.[1-4]

The findings do not suggest major changes to casein, but little attention has been given to this fraction, since it was commonly held that the whey proteins were at fault and research, therefore, was mostly confined to lactalbumin and lactoglobulin.

Although results of clinical or laboratory studies are not detailed, Bray,[5] Evans and Mac Keith,[6] and Stanfield,[7] and several other authorities apparently approve evaporated milk as a hypoallergenic milk.

General Milk Products, Ltd.,
London, W C.2.

R. H WOODCOCK
Manager, Medical Department.

PREPARATION FOR THE PROFESSION

SIR,—I have just read Dr Ellis's erudite article in your issue of Nov 12.

One matter affects students who find academic work difficult compared with brilliant students. This is the inevitable gap between the end of routine clinical appointments and the day of qualification. Once a student has been signed up for all his clinical appointments he seems to be left high and dry, his teachers may take no further interest in his progress—a disheartening situation. Here a well-planned tutorial scheme would have so much to offer. The student, especially the average student, would feel there was someone to whom he could readily turn for help and advice. He should be given guidance in his reading and the tutor should see to it that the student is able to qualify in the shortest possible time.

Has not the time come when one national qualification should be introduced in all our medical schools and which could be operated by all our universities? It could be designated M.B B S England and could be taken in London and the provinces at the same time each year or twice a year. All students would be at an equal advantage, all pursuing the same syllabus. At present chaos reigns in any London medical school, there are students taking finals of at least five different qualifying boards, and at different times of year.

Royal Earlswood Hospital,
Redhill, Surrey

J B GURNEY SMITH

THE CIRCULATING CANCER CELL

SIR,—Your leading article of Aug 27 did not mention radiotherapy as a means of attacking the circulating cancer cell.

Low-Beer[1] was the first to introduce ^{32}P for this purpose. The high doses he advocated were too damaging to normal tissues, especially bone-marrow, and therefore this treatment was suspended. But as you point out the strategic advantage of attacking the lines of communication of these floating cancer cells is too tempting to be abandoned completely. Herzcovitz et al[2] took up the idea in a modified way, introducing a protracted low-dose ^{32}P bath, by giving small doses (200–300 μC) at short intervals.

We have now started in the surgical department of this hospital, under Prof P Nathan a controlled series of breast-cancer cases to evaluate results of this kind of preoperative prophylaxis. More than 50 patients are now being followed up, and the preliminary statistical scrutiny has shown encouraging results.

Beilinson Hospital,
Petah Tiqva,
Israel.

ZYGMUNT LEWITUS
D ROSNER.

THE CASE AGAINST TRENDELENBURG'S POSITION

SIR,—I think it is possible to answer the implied question in your annotation of Nov 26 as to whether Swain's initiative will find favour with the gynæcologists. It has been the general practice at this centre to avoid the Trendelenburg position, the reasons—very similar to those voiced by Swain—being published[3] some years ago under the title "Trendelenberg tilt, an obsolete position". Nevertheless gynæcologists yet remain to give this position up though even proctologists have discovered the joy of more direct vision into the pelvis obtained with the patient horizontal and the relief to themselves of having no longer to operate in scoliotic contortion.

United Birmingham Hospitals,
Birmingham.

J M INGLIS

TREATMENT OF TENSION PNEUMOTHORAX

SIR,—I agree entirely with Mr Macarthur (Nov 26) that no needle will deal adequately with a tension pneumothorax of the type which he describes. But his statement that my spontaneous pneumothorax needle[4] was designed for this purpose is incorrect. It was devised specifically to deal with a spontaneous pneumothorax complicating artificial-pneumothorax treatment. This presented a very special problem which Mr Macarthur may be too young to have encountered. Far from wanting the lung to expand, our aim was to maintain the therapeutic pneumothorax whenever possible, moreover, the fistula in such a case was usually small and would close in a day or so if very little suction was used. The needle did serve a useful purpose in dealing with such cases, and it must be remembered that in those pre-antibiotic days the insertion of a tube into a clean pleura carried a grave risk of infection. I am indeed sorry to hear that the needle is being used for

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[1] Ratner B., Gruehl, H. L. *Amer J Dis Child.* 1935 49 287, *J Amer med Ass* 1935 105 934
[2] Burt, A. R. *Canad. med Ass J* 1940 43, 520
[3] Cutler O I *J Amer med Ass* 1929 92, 964
[4] Eichelberger M *Mod Hosp* October 1938
[5] Bray G W *Practitioner* 1938 141 97
[6] Evans P R, Mac Keith, R. C. Infant Feeding and Feeding Difficulties London 1954
[7] Stanfield, J P *Acta pædiat* 1959, 48 85

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[1] Low-Beer B V A Bell H. G *Amer J Roentgenol* 1956 75 1162.
[2] Herzcovitz A Lupovoc S Rosner D *Vita Medical*, 1956 5 815
[3] Inglis J M., Brooke, N B *Brit med J* 1956 ii 343
[4] *Lancet* 1940 ii, 623

a purpose for which it was not designed I thought that, with the virtual cessation of pneumothorax treatment, it had gone into honourable retirement We no longer possess one at this hospital

Brompton Hospital,
Frimley Branch
Aldershot, Hants
A F FOSTER-CARTER

"RETROGRADE STEP"

SIR,—You report (Nov 19, p 1149) that the Council advising the Home Secretary on judicial corporal punishment considered that its reintroduction would be a " retrograde step "

I have no doubt that this horrible phrase was in fact used as it is beloved by politicians and public figures generally, but in a scientific journal I think it should be printed only in italics or between inverted commas Retrograde is derived from *retro* (backward) and *gradus* (a step), and a " retrograde step " is in my opinion on a par with our old friends the " gastric stomach " and the " cardiac heart "

Bishop Auckland
JOHN M ROBERTSON

CHEST X-RAYS AND RADIATION HAZARDS

SIR,—Although I agree with some of the points made by Dr Beresford (Nov 26), I should like to comment on his references to the use of mass miniature radiography Such general pronouncements are not really helpful since the method of employing units needs to vary so much from area to area, and is indeed always under review by those in charge of units and by the regional hospital boards

In this area we continue to find a worthwhile pick-up rate, above the national average, from amongst the general public and industrial groups, and that is in spite of the very real cooperation we get from general practitioners Our antenatal pick-up rate has also been persistently high, much higher than the figures held by the Adrian committee, in their interim report,[1] to warrant continuation of the routine X-raying of antenatal patients

Court-Brown and others[2] concluded that an increase of leukæmia among children due to radiographic examination of their mother's abdomen during the relevant pregnancy was not established With chest radiography, of course, the dosage received by the fœtus is a fraction of that involved in X-ray pelvimetry I hope, therefore, that obstetricians and general practitioners will not be discouraged, by Dr Beresford's letter, from getting their antenatal patients X-rayed where facilities are available, and especially where it is known that the pick-up rate is high

In 1959 mass radiography produced 37% of the Southampton Chest Clinic notifications, and only 6 out of the 16 cases were general practitioners' referrals Many of these cases would not have been discovered if full use had not been made of the units available

Although we have not had a 35 mm camera unit for many years and their replacements are with 70 or 100 mm units it is a pity to drum them out with malign implications, they have given great service and were a lot more trouble-free than some of the later units In the interim Adrian report the radiation figures for the 35 mm units were certainly as good as and in some cases better than for the 70 and 100 mm units

I agree that all reasonable steps should be taken to reduce radiation figures to the lowest level, and with the use of light-beam defining systems and faster X-ray film we have been able to get readings for the female ovary dose up to 30 times less than the average figures quoted in the interim Adrian report

This is a time when we need to discover every possible case of pulmonary tuberculosis, and the method of using mass miniature radiography for that purpose must be decided locally Finally, is the discovery of other abnormalities so unimportant?

Mass Radiography Centre,
Southampton
M E MOORE

*** The second report of the Adrian Committee was published this week Its recommendations appear on p 1292, and the report is discussd in a leading article in this issue —ED L

NATURAL HISTORY OF STAPHYLOCOCCAL SEPTICÆMIA

SIR,—I stated in the first paragraph of my paper[1] on this subject that some have suggested that this infection is increasing in frequency, but others have denied this In the second statement I referred to Dr Hassall and Dr Rountree as denying this This is an error because they were particularly impressed by the increase in cases of staphylococcal septicæmia from 1951 onwards They were therefore in agreement with our findings in the paper

State University of Iowa
Iowa City
IAN MACLEAN SMITH

TREATMENT OF OBESITY BY THE HIGH-FAT DIET

SIR,—As Dr Sisieni says (Nov 12), it is most important that a diet for the obese should be acceptable both financially and socially, particularly since one's aim is to make the diet a permanent eating habit The low-carbohydrate diet of which we wrote (Oct 29) can fulfil these criteria as least as well as any other diet low in calories

It is understandable that a diet in which the stress is laid positively on unlimited amounts of eggs, meat, cheese, fish, green vegetables, butter, and cream should seem inordinately expensive But in four ways this immediate reaction is misleading Firstly, one often forgets that many people consume a great deal of carbohydrate in quite expensive foods, such as cakes, biscuits, sweets, and chocolates For these people, a change to a low carbohydrate diet may represent a greatly reduced expenditure on food Our patient no 1 spent 12s a week on such items

Secondly, it should be remembered that one essential feature of any long-term dietary regime is that it must be nutritionally adequate It is possible that some patients consume diets with a preponderance of carbohydrate, and with inadequate or at least marginal amounts of some of the nutrients Quite irrespective of dieting, therefore, a doctor who becomes aware that a patient is eating such a diet must advise him to take more of the foods that we have mentioned since they are on the whole foods which supply a greater proportion of the essential nutrients

Thirdly, it should be remembered that the low carbohydrate diet, whilst stressing " unlimited " amounts of carbohydrate-free foods, is in fact self-limiting, as we pointed out this is wh[illegible] it reduces weight Finally, it is not necessary that meat should always be prime steak, or that cheese always be Camembert, or that fish always be salmon there are equally nutritious but far cheaper alternatives

Socially, too, no calorically restricted diet can be more acceptable than a low-carbohydrate diet This point has already been covered in some detail[2]

Consider for example the food which would be eaten at a dinner party by the overweight woman of whom Dr S[illegible] writes She would have the smoked salmon but [illegible] bread She would have the soup but no[illegible] nibble her [illegible]

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1 [illegible] Interim Report of the Comm[illegible] H M S O [illegible] 1959

2 C[illegible] D[illegible] Hill A B *Brit med J* [illegible]

1 *Lancet* [illegible] 1316

2 [illegible]

She would take the meat and green vegetables and—like many of her fellow guests or even her hostess—she would leave the potatoes Since she probably does not go to a dinner party every night, she might just for once have a small portion of the pudding, on the other hand, it may be that she is given fresh strawberries which she can have with cream Or she might content herself with a good portion of cheese but only one biscuit In none of these would she be at all conspicuous Compare her with the obese person eating a diet low in fat no smoked salmon, all the fat carefully trimmed off the meat (unless it is pork, which she would have to refuse), certainly no cream on her strawberries, and certainly no cheese Would Dr Sasieni not agree that the one diet, but not the other, allows an overweight woman to eat in company without " drawing further attention to herself " ?

Queen Elizabeth College,
London W 8

JOHN YUDKIN

SIR,—Dr Sasieni asked for a 1500-calorie diet that is permanently acceptable, both socially and financially, to an adult woman of any age An article on slimming diets in *The Practitioner* of June, 1959, gives full details of such a diet

St George s Hospital,
London S W 1

M E CAREY

A CHILD WITH 49 CHROMOSOMES

SIR,—In examining smears of buccal mucosa of the child with 49 chromosomes described in our article of Oct 22, it was found that a large proportion of nuclei displayed more than one Barr body The frequency distribution was as follows

No of Barr bodies per nucleus	0	1	2	3	4	*Unclassifiable nuclei*	*Total*
No of nuclei	6	18	82	148	14	32	300

The accompanying photomicrograph shows a typical nucleus with three distinct Barr bodies

Cases described of abnormalities of the sex chromosomes seem so far to indicate a relationship between number of X chromosomes (n) and number of Barr bodies in buccal mucosa nuclei, the number of Barr bodies being most often equal to (n–1)

From this it follows that the child in question might have a sex-chromosome constitution of the XXXXY type A point which remains to be investigated is why the sex chromatin in cultured cells of this individual seems to consist of single heteropyknotic masses

Cytogeneticists generally agree that the characterisation of the X chromosomes is difficult, and some authorities[1] believe it impossible

In the present case, by using the criteria on which our previous experience is based, we could not formally label more than 2 chromosomes as Xs We were also inclined to postulate that additional autosomes were present, paradoxically enough because of the severe impairment of the sexual development in our case Thus is seems that individuals with apparent sex-chromosome constitutions of the XXXY,[3] XXYY,[4] and XXXXY/XXXY [5] types mimic patients with Klinefelter syndrome (XXY), at least in the little-altered appearance of the external genitalia

The possibility also exists that X chromosomes when present in excess of the common number may tend to be morphologically abnormal Thus De Carli et al [6] described a woman with 47 chromosomes and a proportion of nuclei with double Barr bodies A formal cytological analysis did not, however, reveal more than 2 X chromosomes, and the extra chromosome was thought to be similar to those of pair no 10 or no 11 An alternative interpretation [7] of these findings is that this extra chromosome represents an X which underwent a deletion

On the other hand, the possibility should be considered that, in our case, autosomes are in fact involved and that their presence in excess may also result in heteropyknotic masses in interphase nuclei

These findings have convinced us that examination of buccal smears is an indispensable aid to a study of any case like this one when the chromosome abnormalities are unusual This is a point about which we have been wrongly sceptical in the past

We wish to extend our warmest thanks to Dr H Klinger, of Basle, who provided us with preparations of the highest technical standard from the buccal mucosa of the patient and who was also responsible for their interpretation and for the photomicrograph

Medical Research Council
Population Genetics Research Unit,
Headington, Oxford

M FRACCARO

Department of Endocrinology and Metabolism,
Karolinska Sjukhuset Stockholm

J LINDSTEN

*** We congratulate Dr Fraccaro and his colleagues on this prompt correction With those noted in our leader of Nov 12 this makes three cases in which extra X chromosomes have been mistaken for other members of the 6–12 group Either the X chromosome is more variable in size than has been thought, or the X chromosomes concerned are abnormal, or our methods are less reliable on this point than we believe Otherwise we must suppose that sex-chromatin bodies can be produced by any extra autosome in the 6–12 group, and this seems unlikely The optimistic supposition of the last paragraph of our leader—that trisomy of every one of the autosomes might some day be demonstrated—was based largely on this case and must unfortunately be moderated —ED L

ANHIDROSIS AND HEATSTROKE

SIR,—I write to support Dr Ladell's views [8] on this subject

In the summer of 1959 Melbourne had its worst heatwave for half a century, with maximum temperatures of 108 5°, 107 3°, 109 0°, and 98 0°F on consecutive days, and this institution for the healthy and infirm elderly was in a state of emergency during this period

A great opportunity for observing the effects of extreme heat on the elderly patient was lost at this time All that was saved were a series of temperature records and some clinical impressions, but these in themselves support the view that it is the rise in temperature which precedes and is a major factor in the cessation of sweating No less than a third of the patients at risk—38 out of a total of 116—had a temperature rise of 1°F or more above normal 9 patients had a temperature rise of 3° or more, the highest temperature being 106 0°F All 9 showed the typical picture of heat hyperpyrexia—hot dry skin, absence of sweating, mental deterioration, and so on Those with lesser degrees of pyrexia did not Careful treatment was successful in all cases

It seemed that the temperature rise came first, and that at a certain level, which varied but was as a rule between 102° and 103°F, something went completely wrong with the temperature-regulating mechanism, and the full picture of heatstroke and anhidrosis developed, with prostration and a rapidly rising temperature

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[1] Patau K *Amer J hum Genet* 1960 12 250
[2] Fraccaro M Lindsten J *Folia hered path* 1960 9 185
[3] Ferguson Smith M A Johnston A W Handmaker S D *Lancet* July 23 1960 p 184
[4] Muldal S Ockey C H *ibid* Aug 27, 1960 p 492
[5] Jacobs P A Buckton, K E , Tough, I , Maclean, N Personal communication, 1960
[6] De Carli L Nuzzo, F , Chiarelli B Poli E *Lancet* July 16 1960 p 130
[7] Jacobs P A Harnden D G , Court Brown W M Baikie, A G *ibid* Aug 13 1960 p 368
[8] *Lancet* 1960 i, 1292

Dr Ladell gives facts relating to the falling off in sweat production with rising body-temperature which fit in very well with our clinical observations, and which would explain our finding that the critical level lay between 102° and 103°F

Greenvale Village for the Aged,
Victoria, Australia
DAVID C WALLACE

CIGARETTES IN HOSPITALS

SIR,—Dr Birch (Dec 3) rightly calls attention to the illogicality of advising patients against smoking and at the same time providing facilities for them to do so Besides vending machines, many hospitals possess a shop or allow the sale of cigarettes to patients by newspaper roundsmen or other means The hospital staff, not unnaturally, also make use of these facilities, thus contributing to the suggestion that the hospital condones something which medical advice often has to condemn

There has also been a growing volume of criticism recently of the lack of central action about cigarette-smoking No-one pretends that this is an easy assignment, but it would seem that the time has arrived when a thorough examination under Government auspices of the various facets of this difficult problem should be undertaken I would suggest that a commission representative of the various medical, educational, and lay aspects be appointed to inquire into the present situation in this country concerning smoking and to make recommendations with a view to safeguarding the public welfare

Clare Hall Hospital,
South Mimms
Barnet
NORMAN MACDONALD

OVERDOSE OF TRIFLUOPERAZINE

SIR,—Attempted suicide by trifluoperazine is unusual, and the following case demonstrates the alarming side-effects of this drug when taken in large quantity

A man of 27 was under outpatient supervision for chronic schizophrenia Several months before admission his treatment was altered to trifluoperazine ('Stelazine') (10 mg daily), which he took conscientiously without ill effect until his supply of tablets became exhausted His mental condition then began to deteriorate and he became depressed and dissatisfied with himself and was unable to concentrate or sleep He consulted a psychiatrist, who prescribed twenty-eight 5 mg tablets of trifluoperazine On returning home, the patient made a determined suicidal attempt by swallowing all the tablets at once 18 hours later he was admitted to this hospital with severe generalised muscle cramps and stiffness of the legs, back, and neck which had developed about 12 hours after taking the tablets On examination he was fully conscious but rolling around the bed complaining of agonising spasms in the back and neck, which tended to subside when he was occupied There was moderate torticollis to the right, with head retraction and stiffness of the neck muscles, but there was no limitation of movement There was slight but definite hypertonus of the right leg with increased knee reflexes and bilateral unsustained ankle-clonus His coordination was good, and pupil reactions were normal with no nystagmus No other abnormal signs were detected in the nervous system

These symptoms were very unpleasant and frightening to the patient but disappeared spontaneously during the next 12 hours without sequelæ They were presumably due to the effects of 140 mg of trifluoperazine on the extrapyramidal system It would therefore seem important that casualty officers should be aware of these side-effects of phenothiazine derivatives and should hesitate to diagnose meningitis, tetany, &c in patients who have taken these preparations

Acute cases should be treated by gastric aspiration and the maintenance of an adequate airway to prevent asphyxiation from spasm of the glottis It has been shown that caffeine benzoate (gr 7½) injected intravenously may be helpful in relieving painful dystonic muscle spasms, and Robertson[1] has suggested that anti-histamines such as diphenhydramine (25 mg) should be given intravenously in all cases of phenothiazine overdosage because of their antiparkinsonian properties

St Mary Abbot s Hospital,
London, W 8
J C BARKER
E M KERR

SAFETY OF IRON PREPARATIONS

SIR,—With the increased use of ferrous salts in the treatment of iron-deficiency anæmias there has been a corresponding rise in the number of children killed by accidental ingestion of these drugs 17 deaths were recorded in Great Britain in 1940–49, and 32 in 1950–53[2] Symptoms of poisoning have been reported as shock, gastrointestinal irritation, necrotic lesions of the stomach and intestine, and damage to the liver and heart[3-5] Intolerance to ferrous salts (nausea, vomiting, and gastrointestinal upsets) have often been reported[6-8]

We therefore thought it important to determine the safety of the more commonly used ferrous compounds when given orally, under conditions which, as far as possible, simulated the accidental ingestion of large numbers of tablets of a commercial preparation

We chose the dog for this investigation because it is possible in dogs to observe subjectively many of the toxic symptoms reported in humans

In our first experiments we compared the safety of ferrous carbonate, ferrous sulphate, and ferrous gluconate after a single large oral dose The animals were killed and examined 24 hours after dosing

The results showed that ferrous carbonate is far less toxic than ferrous sulphate, for example, a dose of ferrous carbonate as high as 1 5 g ferrous iron per kg produced no symptoms of toxicity, nor was there any postmortem or histological evidence of damage to the stomach or intestine In contrast, ferrous sulphate at a much smaller dose of 0 6 g ferrous iron per kg was fatal, and a dose of 0 3 g per kg produced extensive ulceration and inflammation of the gastrointestinal tract Ferrous gluconate, although less toxic than the sulphate, was more toxic than the carbonate, since, although not fatal, it produced gastrointestinal damage at dose levels of 0 75 and 0 375 g ferrous iron per kg

Larger experiments, using commercial tablets of ferrous salts (ferrous carbonate, ferrous sulphate, ferrous sulphate compound, ferrous gluconate, ferrous succinate), confirmed our observations Ferrous carbonate at 1 5 g ferrous iron per kg produced no evidence of toxicity whatsoever, whereas ferrous sulphate (0 187–0 75 g ferrous iron per kg) caused vomiting, ulceration, and inflammation of the stomach, and sometimes inflammation of the duodenum Even with doses as low as 0 012 g per kg there was some damage to the fundus of the stomach The commercial preparations of ferrous gluconate and ferrous succinate also proved more toxic than ferrous carbonate The maximum safe doses of these salts determined by experiments in dogs are

Ferrous carbonate	1 5	g ferrous iron per kg
Ferrous sulphate	<0 012	,,
Ferrous sulphate compound	0 012	,,
Ferrous gluconate	0 017	,,
Ferrous succinate	0 091	,,

Therefore, in our experiments on dogs, ferrous carbonate is 100 times safer than ferrous sulphate, 30 times safer than ferrous gluconate, and 15 times safer than

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1 Robertson W Amer J Dis Child 19[illegible] 100 2[illegible]
2 Report of the Committee on Tox[illegible] J Amer med Ass [illegible] 676
3 F[illegible] G Brit med J 195[illegible] i [illegible]
4 D[illegible] T I D[illegible] A [illegible] J [illegible] 1957 49 1
5 S[illegible] S C[illegible] [illegible]
6 B[illegible] Brit med J 19[illegible]
7 C[illegible] Lancet 195[illegible] i 74[illegible]
8 O S[illegible] D J H[illegible]

ferrous succinate. Because ferrous carbonate has a high degree of safety in these animal experiments and is also clinically effective in the treatment of iron-deficiency anæmias, we believe that the use of a stable preparation of ferrous carbonate, in preference to other iron salts, will help to reduce deaths in children who accidentally take large doses of iron.

It seems that the use of ferrous carbonate would do much to reduce symptoms of intolerance to iron, especially the gastrointestinal upset often reported with other iron preparations.

Research Division,
Allen & Hanburys Ltd.,
Ware, Hertfordshire

P. F. D'ARCY
E. M. HOWARD

DIURETICS IN THE MANAGEMENT OF OBSTRUCTION OF THE SUPERIOR VENA CAVA

SIR,—In patients with bronchial carcinoma causing obstruction of the superior vena cava, there is inevitably an interval between admission to hospital and relief of the obstruction by radiotherapy or alkylating agents; indeed, radiotherapy may temporarily aggravate the obstruction, and several days may elapse before such therapy can even be started.

Six months ago I tried the effect of a diuretic (chlorothiazide) in conventional dosage as an interim measure in these patients. So far this has been tried in 4 patients, and in 2 within twenty-four hours œdema of the face and neck was dramatically reduced, and in the other 2 there was considerable subjective improvement (reduced skin stretching) though no significant objective changes. Diuretics might also be given at the same time as radiotherapy in an attempt to limit local œdema due to heavy irradiation.

Churchill Hospital,
Oxford

D. O. LEWIS

Parliament

Supplementary Estimates

Miss EDITH PITT, parliamentary secretary to the Ministry of Health, said that the whole of the supplementary estimate for the National Health Service[1] related to increased remuneration. For England and Wales £37,665,000 was needed, and most of it—£35,976,000 gross—was for payments to doctors to implement the recommendations of the Pilkington report. The estimate also covered seven other wage awards, of which the largest item was for clerical and ancillary workers.

Dr EDITH SUMMERSKILL was disappointed that this change in pay structure had not been related to the general health of the service. This was probably the last time that such a large sum would be allocated. In future, the standing review body would examine the remuneration of doctors and dentists every three years; this might lead to adjustment of salaries in a minor way, and structural changes might not be so acceptable when there were only minor salary increases. This was the psychological moment for the Minister to say that, as this large sum of money was being given, he wanted the service improved. She was sure that he wanted to save money, and at the same time to do it in a constructive manner. This was his great opportunity, but unfortunately he had missed it. But at least he had said let us have £1 million to improve general practice, and he might now say what he proposed to do with it. She suggested refresher courses, and the reduction of the maximum size of the G.P.'s list. If the Minister wished to reduce the hospital population, he should place more emphasis on the domiciliary services. If he had seized this opportunity to increase the consultants' basic salary, if necessary by abolishing the C Class of merit awards, and to make all domiciliary visits free, then general practitioners could more easily obtain a second opinion. This would help to solve the problem of our overfull hospitals. She also asked why the part-time consultant was still favoured at the expense of the more effective whole-time consultant.

Dr DONALD JOHNSON, too, thought that an opportunity had been missed to reconsider the structure of the service. He wondered whether the capitation fee was the best method of paying the general practitioner. By this method the doctor had only one financial incentive—namely, to get the maximum number of patients. He got no more if he attended them all every day and no less if he sent them all to hospital whether as outpatients or inpatients. He was penalised financially automatically if he spent money on his surgery or employed extra secretarial or nursing assistance. We could talk about developing domiciliary services, but it was the general practitioners who were essentially our agents for providing efficient domiciliary services, and not the local authorities or extensions of the hospital service. Both outpatient and inpatient hospital treatment were largely dependent on how the general practitioner worked.

Mr LAURENCE PAVITT was disturbed that in England £16 million was provided for the regional hospitals, which undertook 90% of hospital care, and £3.7 million for the teaching hospitals, which provided only 10%.

Mr ENOCH POWELL, the Minister of Health, welcomed the Government's acceptance of the Pilkington recommendations, for he believed that it could without exaggeration be said to mark the opening of a new era in the relations between the medical profession, the National Health Service, the Health Ministries, and, indeed, Parliament. It was therefore perhaps a little inconsistent to complain as some speakers had done of lost opportunities, for the essence of the Government's act was the acceptance of the report as a whole. He expected that arrears due to doctors in the hospital service relating to the period back to Jan. 1, 1960, would all be paid before the end of this calendar year, and the full amount of these arrears had been included in the supplementary estimate.

The Next Two General Grants

The Minister of Housing and Local Government has set out his proposals for the general grants to local authorities[1] for the next two years. The Government consider that estimates for total local-authority expenditure for 1961–62 and 1962–63 should be fixed at £818.19 million and £851.15 million respectively (the revised estimates for 1959–60 and 1960–61 were £723.48 million and £769.80 million), and on these figures the Government conclude that the general grant (which is the Exchequer's contribution) should be £454 million for 1961–62 and £472 million for 1962–63.

Local authorities expect to spend on their health services £72.89 million in 1961–62 and £77.20 million in 1962–63 (compared with £64.28 million in 1959–60 and £66.50 million in 1960–61). Discussing these increases the Minister says that because of the new responsibilities which the Mental Health Act will impose on authorities he expects that expenditure on their mental-health services, which had reached about £4 million in 1959–60, will amount to well over £8 million by 1962–63. Other community services for which substantial development has been provided are health visiting, welfare services for mothers and young children, homes for the old and infirm, and welfare services for the physically handicapped. For example, at the end of the current year nearly 38,000 places for the old and infirm which would have ranked for contributions under the National Assistance Act 1948 will have been brought into use, compared with about 30,000 at the end of 1958–59. Estimates for 1961–62 and 1962–63 show that this rate of increase is likely to be substantially exceeded. The number on registers for the handicapped by the end of 1962 are likely to show the following increases over 1959:

Blind and partially sighted persons	7000 (6.2%)
Deaf and hard-of-hearing persons	6000 (17.7%)
Others	24,000 (27.7%)

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[1] See *Lancet*, Nov. 26, 1960, p. 1202.

[1] Local Government Finance (England and Wales). The General Grant Order, 1960. H.M. Stationery Office. Pp. 18. 1*s.* 3*d.*

Academic and Scientific Rates

At the second reading of the Rating and Valuation Bill on Nov 30, Mr HENRY BROOKE, the Minister of Housing and Local Government, said that the Pritchard Committee had recommended that every organisation which qualified as a charity should be absolutely entitled to a 50% remission of rates, whether the benefits it conferred locally were great or small, and that the local authority should have discretion to grant a further remission beyond the obligatory 50% remission, right up to complete exemption from rates The Pritchard Committee was clearly in some doubt about the position of the universities The universities were undoubtedly charities, but they were substantially financed by Exchequer grant through the University Grants Committee Unlike other charities, many of them held a considerable, if not a dominating, position in the towns and cities in which they were established, as well as being different from the ordinary charity in that they were largely Exchequer financed In all the circumstances, it did not seem to the Government that a sufficient case existed for obliging the local authority to give the universities on all their extensive buildings a 50% remission But the Chancellor of the Exchequer was ready to give assurance that any additional rates falling on the universities as a result would be taken into account in determining the amount of recurrent grants to be paid to them from the Exchequer It was simply a question whether the money would come from the tax-payers or from the other ratepayers This applied to all universities and colleges which received grants through the University Grants Committee It did not apply to the Oxford and Cambridge colleges, though it did apply to the university buildings in Oxford and Cambridge The colleges would get the 50%, mandatory relief, because they were charitable foundations and yet did not receive any grant whatever from the University Grants Committee The Government believed that this was the fairest settlement of an intractable problem

The Bill repealed the total exemption from rates given by the Scientific Societies Act of 1843 to societies established for the purposes of science, literature, or the fine arts exclusively The definition in the 1843 Act had proved difficult to apply Under the Bill, practically every organisation which now obtained benefit from the 1843 Act would in future, through being a charity, qualify automatically for 50% derating, and the local authority would have discretion to go further, up to complete exemption Dr REGINALD BENNETT asked whether research associations came under the heading of charities Mr BROOKE said that any organisation, whether a research association or anything else, which could satisfy the authority that it was a charity would qualify

In summing up Sir KEITH JOSEPH, the parliamentary secretary of the Ministry, agreed with several members who had suggested during the debate that it was probable that in the immediate future the impact of the education and health programme would cause the local authority rate demands to rise But the tax-payer was already bearing a substantial share of the cost of these local services and, as the General Grant Order showed, they were still bearing a very substantial share Furthermore rates were the support of local government independence, and everyone wanted to ensure that local government could be vigorous and independent on the basis of its own properly raised, and independently raised, finances

Cleanish Food

On the adjournment on Nov 29, Dr BARNETT STROSS prayed against the new food hygiene regulations (S I 1960 no 1601) which consolidate the earlier regulations and extend them to ' food businesses carried on from homegoing ships and moored vessels He explained he did so only because he thought that they were inadequate He pointed out that the number of outbreaks of food-poisoning had risen steeply and that outbreaks were more frequent in hospitals than in other catering establishments He was especially disappointed that the new regulations still left the responsibility of notifying an infection with the food-handler Dr A D D BROUGHTON regretted that the new regulations did not in any way encourage education in hygiene

Miss EDITH PITT, parliamentary secretary to the Ministry of Health, said that the 1955 regulations had done much to raise the standard of food hygiene, and had proved an effective instrument for enforcing satisfactory basic standards The main emphasis, however, by the enforcing authorities, had naturally been on education rather than on legal proceedings, for the full purposes of the regulations would not be achieved until every food-handler and every customer was so well aware of the importance of good hygiene that correct practices became a matter of course Though there had been an upward tendency in notifications, this might perhaps be the result of a great deal more publicity and far more intensified effort to find out where the cases were People in hospitals were already in a state of susceptibility and there was also more ready notification from hospitals Much was going on in the special training of all hospital staff, catering and nursing, in food hygiene and towards the redesigning of hospital catering facilities—Dr STROSS asked if the hospitals at least could not initiate the examination of food-handlers, but Miss PITT said that examination would be required at such short intervals as to be impracticable She believed that the new regulations should prove an effective instrument for continuing and consolidating the progress achieved since 1955 in this important aspect of modern living

Registered and Enrolled Nurses

On Dec 1 Dame IRENE WARD introduced the Nurses (Amendment) Bill in the House of Commons Its chief purpose is to provide that in future the " roll of assistant nurses " shall be known as the " roll of nurses " and the " assistant nurses " committees of the General Nursing Councils of England and Wales and of Scotland as the " enrolled nurses " committees It also provides that the standard of training required for registration will remain higher than that required for enrolment

QUESTION TIME

R H B Capital Expenditure

Mr J M L PRIOR asked the Minister of Health when he proposed to introduce new methods of allocating finance for capital projects for regional hospital boards—Mr POWELL replied I am reviewing the whole management of the hospital capital programme, but cannot yet say when any changes will be introduced

Group-practice Loans

Mr L A PAVITT asked the Minister of Health how much money, in addition to that already earmarked within the general medical services central pool, he proposed to make available for group-practice loans, following the recommendations of the Pilkington report—Mr POWELL replied £89,000 a year for England and Wales

Means Test for State Scholarships

Mr W F MONTGOMERY asked the Minister of Education whether he was yet in a position to make a further statement on his consideration of the recommendations of the Anderson Committee on grants to students—Sir DAVID ECCLES replied The Government have decided on the general lines of the radical revision of the scale of parental contribution which I announced on Nov 7 The details of this scale, which will come into force in October, 1961, will be published shortly after I have consulted the local-authority associations In addition to university students, the new scale will apply also to students taking comparable courses in further education institutions and to teachers in training No contribution will be required below £700—net scale income—and in general there will be a substantial reduction in the amount which parents will be required to contribute The income-tax child allowance will be continued The cost of the relaxation of the means test now proposed will be approximately £10 million in a full year The system of making awards in Scotland differs in several respects from that in England and Wales, and the application of the Government's decisions to Scotland is still under discussion. Mr MONTGOMERY As we believe in the principle of free secondary education for all, and any child who passes for a grammar school gets a place irrespective of the parents' income, why cannot we transfer this further and give those with the necessary ability a place in further education irrespective of the parents' income Sir DAVID ECCLES This drastic relaxation of the means test is without prejudice to full abolition if on examination it should turn out to be the right thing to do

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Obituary

HAROLD ESMOND ARNISON BOLDERO

Kt, M.A., D.M Oxon, F.R C.P

Sir Harold Boldero, who died at his London home on Nov 30, made great contributions to medical education and to the national organisation of medicine during twenty years as dean of the Middlesex Hospital Medical School and eighteen years as registrar of the Royal College of Physicians of London

Walter Stoneman

Born in 1889, the son of John Boldero, J P, of Mark Cross in East Sussex, he was educated at Charterhouse, Trinity College, Oxford, and the Middlesex Hospital Medical School, where he was a final-year student in 1914 He qualified in the following year and then served in France as a regimental medical officer, in a field ambulance, and as a D.A.D M.S, with the rank of major He returned to the Middlesex in 1919 to complete his medical education and take up junior appointments He was already known as an outstanding athlete, having represented Oxford in athletics in 1911 and in hockey in 1912, and his prowess as a centre-half earned him a place in the England hockey team He soon became known also (even as a house-physician) as an inspiring teacher, and he was one of the first medical registrars to be appointed to the Middlesex.

In 1922 he joined the Middlesex Hospital staff as assistant physician At that time it was customary for the junior physician to take charge of the children's ward, and by most this was regarded as a necessary but not particularly interesting duty But Boldero was fundamentally interested in pædiatrics he had been a clinical assistant at Great Ormond Street and was elected to the staff of the Evelina Hospital for Children in 1921 He had a profound clinical knowledge of the diseases of children and was an excellent therapist But perhaps his greatest asset as a pædiatrician was the way in which he could manage sick children His quiet and gentle manner at once won their confidence, and many of his former colleagues can recall the justified confidence that he inspired in them as parents In 1934, however, he was appointed dean of the medical school and became immersed in administration to an extent that prevented him from developing as a physician and teacher

As the rebuilding of the hospital had just been completed, he began to organise the reconstruction of the medical school, but when the outbreak of war put an end to further building he had been able to complete only one section—that containing the administrative offices and the Boldero library For the next five years he was a sector officer in the Emergency Medical Service, engaged in the organisation of air-raid casualty services, but at the same time ensuring that the Middlesex medical school was kept together as an entity and that medical teaching continued without interruption. It was at this period that Boldero began to show the real greatness of his qualities He had control of every situation and his advice was continually sought in the development and conduct of the service After the war he again led the Middlesex through a difficult period of reconstruction in which the development of the National Health Service brought big administrative changes to both hospital and school He retired from the staff in 1954

A Middlesex colleague writes

"Boldero was an excellent administrator both financially and educationally, and his term of office brought large developments to the school But he did not limit his deanship to the higher walks of administration, he was a personal friend to the students, to whose interest he was genuinely devoted He combined an extreme kindness, and forbearance for human weakness, with rigid principles of conduct. He was held in respect and affection as a man of his word, and his fairness was impervious to any outside influence His great strength lay in his ability to see ahead and to take an objective view, and in his innate honesty of purpose, which was apparent even to those who disagreed most fundamentally with his views He had great courage in all he did, displayed particularly in overcoming the successive personal misfortunes which beset him and the severe illness which struck him down in 1946 The kindest of men and a gay and witty companion, Boldero was a sympathetic adviser to many of his colleagues on a variety of problems, but he could be rigid and inflexible if he considered that basic principles were involved."

The Middlesex was thus for many years the centre of Sir Harold's work and remained perhaps the centre of his interest But, especially after his retirement, other professional bodies claimed his help

He served for many years on the General Medical Council, he was a member of the Senate of the University of London, and he was chairman of the Board of Advanced Medical Studies He was also an original member of the North West Metropolitan Regional Hospital Board, and he sat on many formal and informal committees of the Ministry of Health. Outside the immediate confines of medicine his help was given to the General Dental Council and to the Chartered Society of Physiotherapy He had only lately completed a term of office as chairman of the council of this latter body which had covered the intricate negotiations of the Professions Supplementary to Medicine Act.

But outside the Middlesex his most important work was done through and for the Royal College of Physicians In 1942, after a period as treasurer, he was appointed registrar—an office which gave him scope for his administrative ability With Lord Moran, Sir Russell Brain, and Sir Robert Platt as successive presidents, he took a large share in the negotiations which defined the pattern of the new health service and later modified it. His knowledge and experience of education from his work at his medical school and at the university made him an invaluable adviser, and to this was added a comprehensive and detailed knowledge of the affairs of the college and a willingness to shoulder responsibility

R P writes of the immediate past

"Hal Boldero was 71 He had become a little slower in recent years, and more breathless, but he still had the figure of the athlete he had been in former days and retained a clarity of mind which all who knew him must have envied, though they might be 20 years his junior Confronted with a new project, he would examine it with all the caution of age, wisdom, and experience, but, once convinced, he would work for it with the enthusiasm of a young man Thus he was busy on the plans for the new college to the day of his death, and no-one save the architect himself had done more for them

"The Royal College of Physicians had been his greatest interest since he left the Middlesex, and in recent years he had given nearly all his time to its affairs, but he believed that no man is indispensable and had made it clear more than once that he was willing to resign in favour of a younger man if it were in the interest of the college It never was in the interest of the college, and so he worked on with devotion and I think with much enjoyment until one evening after dining happily with friends he died

"It may be that too few knew him intimately and realised his kindness and the great sense of fun which lay behind his rather dry unemotional facade Those who did will remember not only the respect but the great affection which he inspired in all who worked with him"

W R B recalls memories of a few years ago

"All administrators deal with human nature as their raw material, and necessarily in large measure use similar methods The outstandingly successful administrator must have something more In Boldero this was an unusually selfless devotion to the institutions and organisations he served, and an exceptional power of assessing what was practicable in any situation, having regard to the people concerned, and the restrictions imposed on them by the forces acting upon them

"Before a meeting at which there were likely to be differences of view, one would discuss with him the possible courses of action, and what lines different people would be likely to take The main objective would be laid down, and the steps to be taken, if things went wrong, discussed This was what he called 'doing one's homework' When the committee met, he would stroll in, sit down, and listen If all went according to plan he would probably say nothing If there were strong differences of view he would wait till the main alternatives had been outlined, and perhaps there seemed to be a deadlock Then during a silence he would say quietly and deliberately 'I was just wondering, Mr Chairman ' and then would come one of his masterly understatements, gently deflating an idea, but never a person, and the discussion would take a new turn, and like an ideal three-quarter, he was always in the right place to take a pass If he was ever critical of others (in private) it sprang from his fierce loyalty to the college, and his friends, and his resentment at attacks on either which he considered unfair or underhand He willingly paid the price of this loyalty, which was that sometimes others got the credit which should have been his, and he came in for criticism for things for which he was not responsible

"But beneath the administrator there was a rather shy man, known only to comparatively few To go on an expedition with him, especially to a conference abroad, was to see continuously a side of him of which at other times one only caught glimpses He was an ideal companion, full of gaiety and enjoyment of the quirks of human nature He kept in the background his personal sorrows, and latterly accepted a growing physical disability No man better embodied Osler's ideal of *aequanimitas* We have said farewell to a wise, loyal, gay, and courageous spirit"

Sir Harold's wife died in 1950 after a long illness They are survived by their younger son

A memorial service arranged jointly by the college and the Middlesex Hospital will be held at All Souls, Langham Place, W 1, on Thursday, Dec 15, at 12.30 P M

JOHN MOLYNEUX HAMILL

O B E, B A, M D Cantab, D Sc Lond

Dr J M Hamill, a former senior medical officer of the Ministry of Health, died in London on Nov 29 at the age of 80 He was an authority on food inspection and milk production and did much to raise the standards of food supplies in this country

He was the son of Philip Hamill and a brother of the late Dr Philip Hamill, F R C P From St Paul's School he went to Trinity College, Cambridge, of which he was a scholar He took a first-class in both parts of the natural sciences tripos, and in 1902 he graduated B Sc Lond with first-class honours in physiology He qualified from St Bartholomew's Hospital in 1904 The same year he was appointed Sharpey physiological scholar at University College London In 1906 he took the D P H, and in 1907 the D Sc Lond

In 1907 he was appointed a medical inspector of foods of the special foods branch of the Local Government Board which was being organised by George Buchanan Here Hamill was associated with inquiries into the prevention of food-poisoning and measures for estimating the purity and quality of food-supplies with A W J MacFadden, G W Monier-Williams, G C Hancock, and F J H Coutts, and made a number of reports to the Board on these subjects These investigations were interrupted by the 1914–18 war during which Hamill served as D A D M S (san) in France at G H Q of the British Expeditionary Force and as sanitary officer to the Central Force Headquarters, Horse Guards For this work he was appointed O B E

When the Ministry of Health was established in 1919, he became deputy senior medical officer to the special section of the medical department concerned with the supervision of food-supplies and nutrition, with Dr MacFadden as his senior medical officer Hamill also acted as liaison officer in coordinating the work of this section with the Medical Research Council His report on *Diet in Relation to Normal Nutrition*, which applied scientific knowledge to the selection of food according to nutritional value and cost, was published by the Ministry in 1921 His *Notes on the Pasteurisation of Milk* appeared in 1924 He served on the Ministry's advisory committees on nutrition and on a number of departmental and interdepartmental committees He was British Government delegate to four of the World Dairy Congresses and chairman of the commission which in 1927 inquired into milk production in Holland and Denmark In 1934 he succeeded Dr MacFadden as senior medical Officer of the foods section of the Ministry

A S MacN writes

"Hamill was an excellent medical administrator and an authority on food standards and on tinned foods He was an easy colleague to work with, and his advice was sound and always readily given He was tall and broad in proportion After his war service his health was not good, and in 1940, on reaching the age-limit, he resigned from the Ministry, leaving behind him a record of valuable work on nutrition based on sound physiological principles"

Dr Hamill married in 1932 Miss Lesley Findlater She died in 1957

GEORGE FRANCIS THOMAS SAUNDERS

O B E, M D Dubl

Dr Saunders died on Nov 18 at Kumasi, Ghana, after a motor accident As a specialist in the Colonial Medical Service, he had taken an important part in the control of epidemic diseases in West Africa, and the success of his campaign against sleeping-sickness was an early and valuable demonstration of the efficiency of Western medicine

He served in the ranks in the 1914–18 war before qualifying from Trinity College, Dublin, in 1928 The following year he joined the Gold Coast Medical Service, and of his work there B B W writes "From the first, Saunders' full interest was engaged by the problem of mass disease among rural people, to the exclusion of practice in urban hospitals In the 1920's sleeping-sickness became epidemic in the north of what is now Ghana, but, because of the financial stringency of the depression, he had to struggle with authority until 1936 before he obtained grudging permission to start a control campaign With Dr K R S Morris as entomologist, but otherwise relying only on local Africans, many of them illiterate and none of them having as much as a school certificate, he built up a field organisation which carried the diagnosis and treatment of sleeping-sickness into every village of the affected areas His selection and training methods were so successful that no untoward sequelæ of any of the potentially dangerous procedures used (including lumbar puncture and intravenous tryparsamide therapy) ever arose the epidemic was brought under control in 4 or 5 years, and the good will towards Western medicine which it engendered among primitive people later smoothed the way for the control of other mass diseases among them

'George Saunders was gifted with an extraordinary memory for scientific literature, and his academic knowledge was of a high order He spoke two or three local languages fluently, with a marked Dublin accent. Married to an Ashanti lady since 1930, he retired to live near Kumasi, a rather lonely man since so few Europeans knew of his existence, though deeply admired and loved by those who did know him, particularly the handful of doctors who had seen his work or had been privileged to continue it"

ROBERT RITCHIE SIMPSON

M.B Glasg, F R C S, F R C S.E

Mr R. R. Simpson, who for many years had practised otorhinolaryngology in Hull, died there on Nov 26 at the age of 58

Born at Larkhall, near Glasgow, he graduated M.B in the University of Glasgow in 1923 Soon after qualifying he began training for his specialty, during which time he held junior appointments at the Western Infirmary, Glasgow, and later at Edinburgh Royal Infirmary In 1927 he became F R.C.S E and immediately afterwards joined Mr Ritchie Rodger in private and hospital practice in Hull, subsequently holding many appointments in that city and in the East Riding of Yorkshire. In the 1939–45 war he served as a major in the R.A.M C from 1939-45, first in France until the evacuation of St. Nazaire and later in the Middle and Far East

He was president of the Section of Otology of the Royal Society of Medicine in 1954, and president of the North of England Otolaryngological Society of which he was a founder member In 1954 the Royal College of Surgeons of England elected him to the fellowship ad eundum. He died a week before he would have occupied the presidential chair of the British Association of Otolaryngologists He acted several times as an external examiner in the final examination in surgery at the University of Manchester He served on Hull A Group Hospital Management Committee for many years He was a justice of the peace until four years ago, being particularly interested in juvenile delinquency

Although never working in a teaching hospital, except in his younger days, he retained a deep interest in the University of Hull, particularly in the Departments of Zoology and English, and the shelves of the university library contain some of his books His chief literary contribution was his *Shakespeare and Medicine*, which was published last year

A H writes of one aspect of his work in Hull

"Mr Simpson, along with his colleague and friend Mr Ritchie Rodger, founded and organised the ear, nose, and throat service for schoolchildren in Hull After 1947, when Mr Ritchie Rodger resigned Mr Simpson carried on alone until 1954 when two other consultants were appointed to assist him He was responsible for many improvements in the service, and he was always receptive to new ideas But first and foremost he loved children, and it was because of this that the service at which he had worked so hard was such a successful one He will be sadly missed"

V L tells of a friendship with Mr Simpson dating from 1926 when they were fellow clinical assistants

"It is perhaps his personal qualifications as well as his professional attainments which have made a permanent impression upon my memory I have never met anyone who attracted friendship and affection as readily as Bob Simpson. This is all the more remarkable because he was a man who never courted favour, but was fearlessly, though not aggressively, honest and would stand for truth and justice on all occasions His many friends have admired the courage with which he faced increasing disability During these latter difficult years he had the care of a self-sacrificing wife and the consolation of the background of a very happy family life as well"

Mr Simpson is survived by his wife and by two daughters and a son

JAMES CROLEY SEYMOUR

M.B Lond

J C Seymour, who died at the age of 39 on Nov 28 as the result of a motor accident, had been a Bernhard Baron Research scholar at the Ferens Institute, Middlesex Hospital, London, for the past ten years

He was born in South Africa but came to this country to study medicine After qualifying from St Bartholomew's Hospital in 1945 he held house-appointments at the neurosurgical units there and at Hill End, St Albans

Of Seymour's work at the Ferens Institute T J W writes

"Intellectually well endowed, he was also gifted with hands which made ordinary operating look clumsy and microdissection and manipulation their natural function, while his shrewd clinical sense made clinical diagnosis seem easy Only in the head and neck did anatomical arrangements and physiological derangements prove challenging enough to test his powers of thought and action Intuitively he felt that such conditions as migraine, vasomotor rhinitis, atrophic rhinitis, and Meniere's disease must have common factors, and it was largely at his instigation that the late E R Garnett Passe began sympathetic surgery for inner-ear disorders At the Ferens Institute Seymour made a special study of the inner ear He felt that its unique vascular arrangement might well be Nature's neglected warning system of impending vascular catastrophe and that this could revolutionise orthodox E N T conceptions He also proved that vascular spasm could occur in the inner-ear vessels of animals He correlated this with his neurosurgical experience of human carotid and cerebral artery spasm and advocated strongly the need for vasodilators, sympathetic block, or even sympathectomy in those cases Nearly ten years ago he first mooted the possibility of the beneficial effects of sympathectomy for atrophic rhinitis and of parasympathectomy for vasomotor rhinitis Much that he said then is beginning to find acceptance today

"To those who did not know him his rather disdainful air, cutting tongue, and obvious intellectuality were barriers difficult to overcome The real man, however, was a very different and altogether delightful person who enriched the lives of those few lucky enough to be his friends Full of stimulating ideas, considerate, witty, and above all supremely sensitive and sympathetic to those around him he was very far removed from the coldly scientific research worker he made out to be Swimming, motor racing, and latterly fishing were his relaxations and in each he was a perfectionist To those who knew and loved him, the world will be a much less stimulating place without James Seymour "

Mr W W GALBRAITH

W T I, who as a young surgeon worked under Mr Galbraith during his last year as senior surgeon at the Western Infirmary, writes

"Although in his last months of active surgical life, Mr Galbraith's interest in everything appertaining to surgery was immense As well as being a very great technical surgeon himself, he loved teaching operating surgical techniques to his juniors, and the hours spent with him remained memorable to the many young men he trained Though at the end of a long and distinguished urological career, he was remarkably openminded and receptive of new ideas with the happy knack of discerning what was unsound or not practical

"We were all stimulated by his enormous zest for life and his interest in everything medical in the widest sense There was nothing narrow or departmental in his approach to surgery, and no man could have been more generous in spirit to his colleagues Especially did he delight in seeing young men advancing in their professional life, and the loss of his enthusiastic encouragement will be felt by many young surgeons both here and abroad Nor was this kindly interest limited to the surgeons he trained He took a pride in the careers of the girls who worked under him as nurses, sisters, and secretaries, and was always ready to help them in any way he could It is a measure of his greatness and warmth of heart that his passing has caused such sadness in so many varied walks of life "

Public Health

Scottish Health Statistics

The Department of Health for Scotland have published the second[1] of their new series of annual reports giving details about health and health services in Scotland The report includes statistics of population, morbidity and mortality, sickness among the insured population, maternity services, infant and child health, general medical, dental, and ophthalmic services, hospital and specialist services, and cost of the health services

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[1] Department of Health for Scotland Scottish Health Statistics 1959 H M Stationery Office Pp 196 21s

Infectious Diseases in England and Wales

Disease	Week ended November			
	5	12	19	26*
Diphtheria	4	1	2	1
Dysentery	422	413	492	496
Encephalitis				
Infective	3	3	2	2
Postinfectious				1
Food poisoning	161	210	151	302
Measles excluding rubella	5283	4869	5412	5554
Meningococcal infection	18	27	13	12
Ophthalmia neonatorum	26	17	22	13
Paratyphoid fever	2	4	4	7
Pneumonia primary or influenzal	215	232	284	291
Poliomyelitis				
Paralytic	8	8	11	8
Non paralytic	2		4	1
Puerperal pyrexia	175	174	133	197
Scarlet fever	416	436	499	569
Smallpox				
Tuberculosis				
Respiratory	363	348	399	375
Meninges and C N S	6	4	4	10
Other	51	41	52	41
Typhoid fever	2	2	5	3
Whooping-cough	1000	935	1055	1105

* Not including late returns

Diary of the Week

DEC. 11 TO 17

Monday, 12th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road W 12
4 P M Prof D V Hubble Steatorrhœa in Childhood

Tuesday, 13th

ROYAL COLLEGE OF SURGEONS OF ENGLAND Lincoln s Inn Fields W C 2
5 P M Dr M S Israel Chronic Inflammatory Lesions of the Small Intestine (Erasmus Wilson demonstration)

ROYAL SOCIETY OF MEDICINE 1, Wimpole Street W 1
5.30 P M *Experimental Medicine and Therapeutics* Dr A Spinks Dr D R Laurence Transfer of Drugs from the Animal Laboratory to Man
8 P.M *Psychiatry* (Joint meeting with the Medico Legal Society) Dr Northage de Ville Mather, Mr Henry Elam Medical Evidence and its Presentation in Court

INSTITUTE OF DERMATOLOGY, Lisle Street W C.2
5 30 P M Dr R H Marten Moniliasis

BIRMINGHAM MEDICAL INSTITUTE 36, Harborne Road Birmingham
8 P M *Psychiatry* Mr J G Hamilton Surgical Treatment of Intractable Pain

MANCHESTER MEDICAL SOCIETY
5 P M (Clinical Sciences Building York Place) *Surgery* Mr Rodney Smith Expanding Scope of Hepatic Surgery

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5 15 P M (General Infirmary at Leeds) Mr Douglas Northfield *Tumours Involving the Floor of the Third Ventricle*

Wednesday, 14th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Mr Owen Daniel Complication of Diversion of the Urinary Stream (Hunterian lecture)

ROYAL SOCIETY OF MEDICINE
4 30 P M *Physical Medicine* Dr B G B Christie, Dr R W Gilliatt, Dr A L Woolf Electrodiagnosis

INSTITUTE OF DERMATOLOGY
5 30 P M Dr R W Riddell *Subcutaneous and Systemic Mycoses*

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S W 3
5 P.M Dr J R May Considerations Regarding Immunity to *Hæmophilus influenzæ*

EUGENICS SOCIETY
5 30 P M (Burlington House Piccadilly, W 1) Dr A C. Stevenson Modern Trends in the Population Genetics of Man

HARVEIAN SOCIETY OF LONDON, 11 Chandos Street, W 1
8 15 P M Dr S C Truelove Ulcerative Colitis

MANCHESTER MEDICAL SOCIETY
5 P M (Medical School University of Manchester) *Pathology* Dr L L R White Histopathology of Virus Infections

Thursday, 15th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P M Dr Leslie Turner Structure of Arachnoid Granulations with Observations on their Physiological and Pathological Significance, *(Arris and Gale lecture)*

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
11 15 A M (Queen Charlotte s Hospital Goldhawk Road W 6) Mr J Marshall Scott Problems of the Occipito-posterior Position

NUFFIELD ORTHOPÆDIC CENTRE, Wingfield Morris Orthopædic Hospital Oxford
8 30 P M Prof Joseph Trueta Account of Visit to Orthopædic Centres in the United States of America

Friday, 16th

UNIVERSITY OF LONDON
5 P.M (University College Hospital Medical School University Street W C 1) Dr E H Kass Pathogenesis of Pyelonephritis

FACULTY OF RADIOLOGISTS
1 30 P M (Joint two-day meeting with the British Institute of Radiology and the R S M Section of Radiology at 1 Wimpole Street W 1) Prof Sheila Sherlock Dr W B Young Mr H S Williams Dr Stanley Shaldon Sir Roy Cameron Diseases of the Liver

ROYAL SOCIETY OF MEDICINE
5 30 P M *Epidemiology and Preventive Medicine* Prof Thomas McKeown Dr C. O Carter Congenital Pyloric Stenosis
8 P M *Pediatrics* Dr B E Schlesinger Course and Treatment of Still s *Disease (Presidential address)*

ROYAL COLLEGE OF SURGEONS OF EDINBURGH Nicolson Street Edinburgh 8
3.30 P M Prof D F Cappell Points in the Diagnosis of Certain Tumours of the Skin

Saturday, 17th

FACULTY OF RADIOLOGISTS
10 A M *(Joint meeting continued at the Royal College of Surgeons)* Prof R B Lucas Dr E L Ingram Mr H P Cook Sir Stanford Cade, Prof B W Windeyer Tumours of the Mandible

Appointments

CARUANA SALVINO A M D B SC Malta D T M & H, D P H assistant M O, Cheshire

EYRE WALKER D W M B N Z F F A R C S D A part time consultant anæsthetist Stafford hospital group

H[illegible] O I I M B Lond assistant M O Hertfordshire

JOHNSTON M W M D Belf F F A R C S D A part time consultant anæsthetist United Manchester Hospitals teaching group

JONES R I M B L pool D P H deputy M O H and deputy principal school M O Denbighshire

Manchester Regional Hospital Board

HALL M H M R C S senior casualty officer Preston Royal Infirmary

MACMILLAN J B M B Glasg F R F P S consultant dermatologist, Blackpool and Fylde Preston and Chorley Blackburn and District and Burnley and district hospital groups

T[illegible] J R M R C S, D P M assistant psychiatrist Lancaster Moor Hospital

Notes and News

HOSPITAL COSTS

THIS is the third year of the new detailed system of hospital costing, and for the first time the returns[1] of the 350 selected large hospitals are published in three parts

Part I contains a cost summary (showing the inpatient cost per week and, except for long-stay hospitals, the cost per case), together with separate costs for wards and outpatient (including casualty) departments Part II gives detailed costs for seven lay departments (e g , catering, boiler house, laundry) and part III for four medical departments (e g , diagnostic X-ray, pathological laboratories) Expenditure of each separately costed department is expressed in terms of costs per unit of work performed The cost unit used depends on the function of the department—thus, catering costs are expressed as costs per person fed per week

The remaining 2000 N H S hospitals in England and Wales use a less detailed system of costing, and their returns will not be published centrally as in previous years But each regional hospital board will compile the figures for its own hospitals and exchange them with other boards, so that the details can be generally available within the service National average costs for these hospitals are included in part I of the returns

On average, costs per patient per week rose in 1959–60 by rather more than 8% An increase of about 6% can be accounted for by increased wage-rates, the cost of reducing hours for nurses and ancillary workers, and price-changes The cost per case treated increased on the whole by much less than the weekly cost, suggesting that beds are being used more intensively

For acute hospitals the average net inpatient cost per week was £22 5*s* 3*d* for 1959–60 (compared with £20 11*s* for 1958–59) and the net inpatient cost per case was £60 17*s* 8*s* (£58 11*s* 11*d*) Comparable figures for London teaching hospitals were £36 6*s* 8*d* (£34 13*s* 6*d*) and £82 13*s* 5*d* (£80 17*s* 1*d*)

THE HOSPITAL VISITOR

IN public administration, hospital management committees are *sui generis* the members are not elected, they do not strictly represent any organisation, and, though committees spend large sums every year, no sanctions can be applied to individuals for any financial misfeasance Ideally, perhaps, each committee should comprise a cross-section of the population of the area it serves, and members may be expected to make some contribution from their experience elsewhere to the wellbeing of the hospital service Like the average patient, the new member enters a new world, and must expect a period of bewilderment, but it will be shortened for him if he studies two booklets lately issued in revised editions

The first of these[2] is by Mr Stuart-Clark, now senior tutor at the Hospital Administrative Staff College established by the King's Fund and formerly chairman of a large hospital group in the Metropolitan area He outlines the history of hospital administration before 1948 and the position of the management committee within the service In discussing the various committee structures he emphasises that no group can perform its function properly without full and efficient medical advice, and that " the group medical advisory committee is the accredited adviser on all medical matters " The feeling of frustration which often affects members is not overlooked one experienced person is quoted as saying that he always asked himself after a meeting what specific action would have been taken and what mistake would have been avoided if there had been no meeting, and the answer was often disappointing The responsibility of members towards complaints is considered many of these may prove frivolous, but others must be fully investigated so that necessary action may be taken without delay

Visiting the hospitals is an important part of members' duties, to obtain both first-hand information on the services provided and personal knowledge of the staff employed Guidance on this is given in the second booklet,[3] which was originally based on the great experience of King's Fund hospital visitors The statement that on going round the hospital it is " inadvisable " to discuss matters of policy with members of the staff will be interpreted as a piece of understatement or meiosis gossip and the grapevine are indigenous growths in hospital premises, and joint staff advisory committees, both medical and lay, are the right places for discussions of policy But very useful suggestions are made about the questions that will be helpful when examining each major department, and some guidance is given on approved modern practices The new member, and perhaps the oldest too, will find that both booklets provide a pleasant epitome of what the lay visitor ought to know and ask

THE CONGO

AFTER returning, at the end of last month, from his third visit to the Congo, Dr M G Candau, director-general of W H O , expressed satisfaction that the health situation there had been maintained at a reasonable level This was due, he said, to the unremitting efforts of Congolese health workers as well as to the international contribution made by Government, Red Cross, and Red Crescent medical teams But the emergency was not yet over The presence of the medical teams gave a welcome breathing-space while W H O recruited 130 medical staff In Dr Candau's opinion the most important form of assistance that W H O was rendering to the Congo was the long-term training programme for Congolese doctors, of whom there was not one when the country became independent last July 60 Congolese medical assistants were now in training for medical degrees in France, at the Universities of Rennes, Nantes, Bordeaux, and Montpellier These medical assistants had already undergone four to six years' medical training, and many had had several years' practical experience Accordingly they should be able to qualify fully within three years, when, together with fresh medical graduates of the Lovanium University (near Leopoldville), they would constitute the backbone of the future Congolese health services In addition 7 Congolese undergraduates had been placed at medical schools in Europe (4 at Geneva and 3 at Lyon), and would qualify in six years W H O was strengthening the medical faculty of Lovanium University, and it had given a few fellowships for special studies, such as medical entomology

HOSPITAL ALMANAC

EACH year the Institute of Hospital Administrators offers those who share its interests a convenient and comprehensive survey[4] of the hospital world and a good many of the facts needed to keep it turning Inevitably there is a certain sameness about a reliable compilation of this kind (this year's chief novelty is the expansion and rearrangement of the Northern Ireland section), and most of the yearbook is for reference rather than reading The editor's introductory review of progress and problems is always an interesting exception, and this year those who settle down to it without delay will find a sensible discussion of the practical implications of the new Mental Health Act for the hospital psychiatric services, a suggestion that though work study is growing it is more likely to bring increased efficiency than financial saving, and a firm reminder that even the present intensive hospital-building programme is inadequate to make good twenty years of arrears Nor is building going on fast enough to satisfy Mr Milne The time now taken to bring a hospital project from conception to completion is in his view " ludicrously long " The remedy in his realistic view is the acceptance of some measure of standardisation of design and costing

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[1] National Health Service Hospital Costing Returns year ended March 31, 1960 Parts I II and III 1 guinea each H.M Stationery Office

[2] Administering the Hospital Group the work of the management committee member By A C STUART CLARK M.A., senior tutor Hospital Administrative Staff College formerly chairman Wandsworth Group Hospital Management Committee London Institute of Hospital Administrators (75, Portland Place, W 1) 2nd ed. 1960 Pp 64 3*s* 9*d* (post free 4*s*)

[3] Hospital Visiting manual for members of hospital management committees and house committees when visiting hospitals From King Edward s Hospital Fund for London 34 King Street, E.C 2 1960 Pp 52 2*s* (post free)

[4] Hospital Year Book 1961 Editor J F Milne, M C. B Sc (Econ) Pp 1194 59*s* 6*d* (postage 2*s* 3*d*) From the Institute 75, Portland Place London W 1

CANADIAN MEDICAL RESEARCH COUNCIL

The National Research Council of Canada has set up a Medical Research Council with responsibility for all activities formerly conducted by the N R C's division of medical research The new Council, which will have virtually complete autonomy in its operations and full responsibility for policy but will be under the general administration of the N R C, has been created as an interim measure pending the Canadian Government's consideration of appropriate legislation The eventual establishment of a completely independent medical research council was implied in a Ministerial statement in the Canadian Parliament last summer

Dr R F Farquharson, professor emeritus of medicine at Toronto, will be chairman of the Council, and Dr J Auer, professor of anatomy at Ottawa, will be secretary The other members will be Prof Louis B Jaques (Saskatchewan), Prof Roger W Reed (McGill), Dr Chester B Stewart (Dalhousie), Prof Malcolm Brown (Queen's), Prof Marvin Darrach (British Columbia), Prof Roger Rossiter (Western Ontario), Prof J Doupe (Manitoba), Prof A L Chute (Toronto), Dr Rosaire Gingras (Laval), Prof Walter C MacKenzie (Alberta), Prof F C MacIntosh (McGill), Prof L P Bouthillier (Montreal), and Prof H E Taylor (British Columbia)

EXPIRED-AIR RESUSCITATION

The British Red Cross Society have issued a memorandum on expired-air resuscitation Drawn up by their medical adviser, Major-General F C Hilton-Sergeant, this is commendably brief and practical After a short introduction, the mouth-to-mouth and the mouth-to-nose methods are clearly described The difficulties and dangers of the methods are fairly set forth, and the circumstances in which they may be used are outlined A few sentences are devoted to mouth-to-airway and mouth-to-mask procedures, and reasons why the society does not recommend them for ordinary first-aid workers are given The memorandum concludes by emphasising the importance of a clear airway for any method of artificial respiration, and saying how this may be achieved

Methods of expired-air resuscitation do not at present form part of the Society's training syllabus, but this memorandum is a valuable contribution which should receive wide publicity Copies may be obtained from the Stores and Supply Department, British Red Cross Society, 14, Grosvenor Crescent, London, S W 1, at 2*d* per copy (postage extra)

NEW PROCEEDINGS

As Lord Adrian has lately pointed out,[1] our learned societies, through their meetings, publications, and libraries, are an important forum for the interchange of ideas Because they realised that the lack of a journal was a severe handicap to a scientific society the Association of Chemical Biochemists from their inception included in their rules power to set up a journal Till now, for lack of money, this has taken the modest form of a cyclostyled *Newsletter*, but this year they have felt able to afford more formal print, and the first issue of their *Proceedings* has appeared Besides reports of regional meetings and book reviews, it contains a symposium on congenital adrenal hyperplasia The *Proceedings* will be published quarterly (annual subscription £1, single copies 6*s*) Contributions and orders should be sent to the hon editor, Mr H Varley, M SC, F R I C, department of chemical pathology, Royal Infirmary, Manchester, 13

University of Birmingham

Mr R L Edwards has been appointed senior lecturer and first assistant in the department of obstetrics and gynæcology

University of Wales

At recent examinations for the degrees of M B, B CH the following were successful

Elizabeth K M Archer P G Cunningham Davis D G Daniels B F Deere W D Edwards J N I Hughes R H Hughes G D Isaac [illegible] Jayasinghe [illegible] M Jones T T Jones [illegible] M L Lloyd [illegible] [illegible] M J G [illegible] H A [illegible] A G W[illegible]

Royal College of Surgeons of England

The Lister medal for 1960 has been awarded to Prof Wilder Penfield, director of the Montreal Neurological Institute in recognition of his service to the advancement of medical and biological knowledge Professor Penfield will give the Lister lecture at the college on April 5

Royal College of Surgeons in Ireland

On Dec 2 the fellowship of the college was conferred on Peter Chee Nam Wong, and licences to practise were conferred on the following who have passed the final examinations of the Conjoint Board in Ireland

Edith M B Drohan M T R Collins Eugene Curran I G Fleming B E Gittens C F Kelly, Kim Lan Lim Patrick Lowe Jasswanti Lu[illegible]h mun Harold Morris Delia T McCartan Savathrey Naidoo P D O Brien Samuel Asare Odel P J O Grady Olatewaju Olasimbo D A J O Neill Harripersach Sanhue

Postgraduate Medical School of London

An advanced symposium on selected topics in chemical pathology will be held from April 18 to 20, at the Postgraduate Medical School, Ducane Road, W 12 Further details will be found in our advertisement columns

Royal Society

At the anniversary meeting of this society on Nov 30 Sir Howard Florey was elected president in succession to Sir Cyril Hinshelwood Among the other medical fellows Sir Lindor Brown was re-elected biological secretary, and Dr R G Macfarlane was elected a member of the council

Royal Society of Health

Sir Arthur Massey is to become chairman of the council of the society on Jan 1

European Colloquium on Endocrinology

This colloquium, which is to be organised by the Association Médicale France-Espagne and the Medical School of Barcelona, will be held from May 20 to 22 at San Jorge on the Costa Brava Further particulars may be had from Prof J M Cañadell, Avenida Generalísimo, 497, Barcelona 15, Spain

Heberden Society

On Dec 2 the Heberden oration was given in London by Dr J J Bunim, of the National Institutes of Health at Bethesda, Maryland He spoke on Sjögren's syndrome and its pathogenetic implications

The society's dinner in the evening at the Zoological Gardens was the largest it has had In proposing the main toast, Lord Nathan touched on historical events affected by disease and on the influence of doctors exerted through their patients Dr F Dudley Hart, the president, said that members of the society were united by a common interest in rheumatism but were drawn from a great variety of specialties, from orthopædics to biochemistry His speech concluded with the presentation of the Heberden medal to Dr Bunim Dr Oswald Savage proposed The Guests (who included Dr F Forestier, of Aix les Bains, and Prof J Goslings, of Leiden), and Dr T F Fox replied

British Society for Hæmatology

This society was inaugurated at a meeting on Nov 19 at the London School of Hygiene and Tropical Medicine when a symposium on leukæmia was held The second meeting will take place in Oxford on April 8 under the chairmanship of Prof L J Witts Membership is open to scientists and doctors engaged in the study and practice of hæmatology The provisional secretary is Dr Rosemary Biggs, Blood Coagulation Research Unit Churchill Hospital, Oxford

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A meeting of the Osler Club will be held on Tuesday, Dec 13, at 8 P M, at the Royal College of Physicians, Pall Mall East, London, S W 1, when Dr C E Newman Prof R Weiss and Mr A C Crombie will speak on Thomas Linacre (1460–1524)

The Hospital Personal Aid Service for the Elderly, which is run by King Edward's Hospital Fund for London has moved to 21 London Bridge Street London, S E 1 The Elderly Invalids Fund is also at this address

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[1] See *Lancet*, Nov 19 1960 p 1149

The Lancet · Saturday 17 December 1960

ARTERIAL REPLACEMENT AND RECONSTRUCTION

A Five-year Review

David J Tibbs
M C, M S Lond, F R C S
READER IN SURGERY, UNIVERSITY OF DURHAM, HONORARY CONSULTANT SURGEON, ROYAL VICTORIA INFIRMARY, NEWCASTLE UPON TYNE

Methods of arterial replacement and reconstruction have passed the stage of enthusiastic but sometimes ill-judged usage and are now being critically appraised Sufficient experience has been gained to predict the likely outcome of any procedure over the ensuing year or two, and soon unsatisfactory results will be due to bad selection of patient or procedure or both

This paper describes five years' experience of these methods in the professorial surgical unit of the Royal Victoria Infirmary The review covers the *total* experience with arterial replacement and reconstruction during that time except that repairs of recent arterial injuries and embolectomies are excluded since these have been reviewed elsewhere (Hardy and Tibbs 1960, Tibbs 1960) The comparatively small number of patients involved has facilitated complete follow-up The main aim has been to determine the factors leading to success or failure in the different procedures

In the past five years, planned gradual development of arterial surgery has taken place in this unit In the first three years homografts were employed almost exclusively, in the past two years woven or knitted crimped ' Dacron ' (' Terylene ') prostheses have been used for all arterial replacements, but recently thromboendarterectomy has been performed with increasing frequency for arterial reconstruction, particularly of major abdominal arteries

Table I shows the disorders in the 116 patients in this series

Materials for Arterial Replacement

Between 1955 and 1958 the arterial homografts used for arterial replacement were prepared by immersion for 48 hours in an antibiotic solution (Fisher et al 1956), freeze-dried (Eastcott et al 1954), and stored in evacuated tubes (Flewett et al 1955) This process was very convenient and ensured adequate sterilisation

Table II summarises the main complications attributable to the homograft Of 40 homografts no less than 5 gave way In each case there was evidence that the graft had leaked or ruptured where graft substance was sutured to graft substance—for example, where a suture line repaired a defect in the homograft This weakness is understandable since the freeze-dried graft is dead tissue and a suture line within it is not bridged by living tissue for many months, it is only ensheathed, and this may provide inadequate support

Many homografts closed off and specimens could be obtained occasionally at a further operation or, in 1 patient who died from a different condition, at necropsy In the homografts that had closed a thick deposit of fibrinous material, indistinguishable from atherosclerosis, overlay the original intimal layer, and this accords with Duguid's theory of the development of atherosclerosis (Duguid 1946, 1948, 1955) In the first two years this was the only process observed, but later two homografts removed after functioning for four years both showed gross atheromatous change—i e, thick yellow areas of fatty deposits with deformity and narrowing of the grafted artery, microscopically the graft showed extensive vascularisation with hæmorrhages under existing plaques, again supporting Duguid's (1960) beliefs

TABLE I—CONDITIONS FOR WHICH ARTERIAL RECONSTRUCTION OR REPLACEMENT WAS UNDERTAKEN IN 116 CASES

Condition	No of cases
Abdominal aortic aneurysms	24
Occlusion of abdominal aorta and/or iliac arteries	33
Occlusion of lower-limb arteries	45
Miscellaneous	
Aneurysm—	
Subclavian (cervical rib)	1
Femoral	5
Popliteal	1
Traumatic arteriovenous fistula	1
Internal-carotid artery narrowing	5
Renal artery narrowing	1
Total	116

Our experience, therefore, like that of other workers, showed that the homograft tended to be weak at points where it was sutured to itself and that it was liable to participate actively in the progress of atherosclerosis (Szilagyi et al 1957) We doubt whether any method of preparing the homograft is immune from these changes

TABLE II—COMPLICATIONS DUE TO ARTERIAL " GRAFT " ITSELF

Material	Total no of grafts	Time of onset of complication	Complication	Outcome
Homograft	40	3rd day	Leakage from suture line in graft (femoral)	Repaired successfully
		1st week	Leakage from suture line in graft (femoral)	Graft replaced successfully
		2nd mo	Aneurysm around graft (iliac)—early in series	Replaced further leakage, ileus, death
		8th mo	Leakage into duodenum from sutured defect in graft (aortic)	Repair but embolus dislodged from thoracoabdominal aneurysm, mesenteric infarction death
		11th mo	Leakage from graft (femoropopliteal)	Repair, but thrombosis of graft amputation (indicated originally but postponed by graft)
Orlon	2	5th mo	Abscess around abdominal prosthesis (aortic)	Drained, leakage from suture line, repaired, leakage from another suture line, death
Dacron	50	2nd mo	Staphylococcal infection of bifurcated aorto-iliac prosthesis (Leriche syndrome)	Prosthesis removed, patient reverted to pre graft state
		5th mo	Rejection of prosthesis from outset recurrent massive effusion which ceased immediately prosthesis removed (femoropopliteal)	Prosthesis removed limb survived

These observations, combined with the obvious difficulties of collecting homografts from cadavers, led to our abandoning this form of arterial replacement, and we now avoid the homograft, since it lacks durability.

Fortunately other means of arterial replacement were available. The advantages of the crimped woven or knitted dacron arterial prosthesis had already been demonstrated (Crawford et al. 1958, Julian et al. 1959), and from 1958 these arterial substitutes were routinely used by us whenever an artery had to be replaced or bypassed. (Two 'Orlon' bifurcated aortic prostheses were used in 1956.) We have found the change beneficial, no case of leakage or rupture of the prosthesis or its anastomosis to the patient's arteries has occurred (table II). Leakage through the material of the prosthesis at the time of insertion has not proved a problem because a routine was early established of anastomosing the upper end of the prosthesis to the patient's artery and allowing short bursts of arterial blood to flow into the prosthesis until it was entirely leak-proof; alternatively, the effectiveness of preclotting was tested by introducing blood from a syringe under pressure into the prosthesis. Infection, although uncommon, has been the most alarming complication with the orlon and dacron prostheses (see table II). In 1 patient, sterile fluid leaked for two months from a sinus overlying the prosthesis before breakdown of an anastomosis necessitated its removal. This may have been due to host rejection of the plastic material rather than sepsis; the prosthesis had been washed in cetrimide—a practice to be avoided. Sepsis is dangerous to any arterial "graft", and our experience is not an argument against plastic prostheses, but rather a reason for not inserting any foreign material if the patient's own arteries can be reconstructed. This is one reason why in the abdominal arteries thromboendarterectomy is preferable to arterial replacement.

Late occlusion was not more frequent in the crimped dacron prosthesis than in the homograft, and in those cases where a specimen of the dacron prosthesis was obtained after its closure the plastic tube showed thick deposits of atherosclerotic material on its inner aspect. The gross atheromatous changes observed in homografts after four years have not yet been encountered, and the immunity of the dacron prosthesis to late vascularisation in its wall may protect it from the severe late degenerative changes which occurred in homografts. But until effective methods of controlling atherosclerosis are developed, no "graft" or reconstruction can escape narrowing by the fibrinous deposit characteristic of the disease. The difference between the thick opaque pseudo-intimal layer formed inside a dacron arterial prosthesis in the atherosclerotic patient and the transparent pseudo-intima of a prosthesis in the healthy animal is striking.

We have frequently observed that the dacron prosthesis adheres only lightly to its surrounding fibrous sheath and to its pseudo-intima, both shortly after insertion and later. The dacron tube is not intimately incorporated in the tissue and acts merely as a conduit lined by cells laid down by the blood-stream and by ingrowth from each end. The strength of the new vessel depends entirely on the fabric of the prosthesis, and how long this remains unimpaired is still unknown; theoretically the easily detached internal layer seems vulnerable but we have not as yet encountered a "graft" failure which could be ascribed to its detachment.

Our general conclusion is that the crimped dacron (terylene) prosthesis (and presumably 'Teflon' as well) is to be preferred to the homograft because of its greater durability, but any form of arterial "graft" should be avoided whenever there is an acceptable and equally effective alternative.

Abdominal Aortic Aneurysm

The term "abdominal aortic aneurysm" in this paper refers to a distinct expansion of the infrarenal portion of the aorta, readily palpable through the abdominal wall; the aneurysms found at operation had diameters at least four times as great as that of the normal aorta. Prominence or tortuosity of the aorta was not considered sufficient reason for operation.

Fig. 1 shows the results obtained by treating both ruptured and unruptured abdominal aortic aneurysms by replacement with a "graft". Details of postoperative deaths are summarised in table III, which shows that resection and replacement of an unruptured aneurysm with a "graft" (dacron for preference) carried a low mortality-rate; the figures for long-term survival compare favourably with the data of Estes (1950) and Barratt-Boyes (1957) for untreated aneurysms. As regards leaking or ruptured aneurysms, the value of operation is shown by

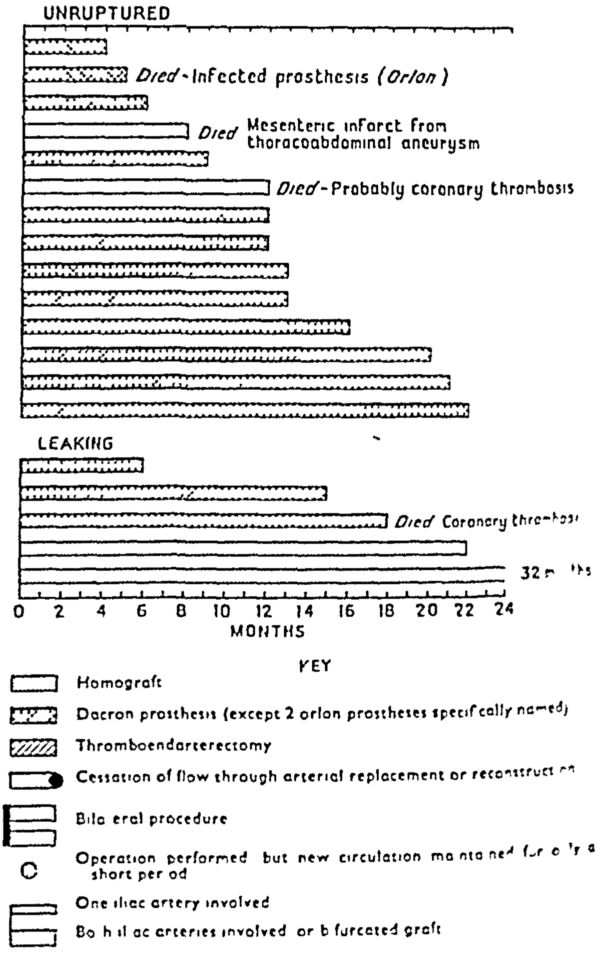


Fig. 1—Progress of patients operated on for aneurysm of the abdominal aorta between September 1955 and July 1960.

In this and in the succeeding figure each bar represents 1 procedure and, except where indicated, 1 patient. The length of each bar corresponds to the number of months from [illegible] operation until July, 1960, or until the cessation of flow through the arterial replacement or reconstruction, unless termination [illegible] (see key) is specifically indicated; circulation through the [illegible] replacement or reconstruction continued [illegible] on July 1, 1960. Patients who died in hospital postoperatively are shown in table

TABLE III—ANALYSIS OF DEATHS IN HOSPITAL FOLLOWING OPERATION FOR ARTERIAL REPLACEMENT OR RECONSTRUCTION

Condition for which operation performed	No of cases	No of deaths	Comment
Abdominal aneurysm			
Unruptured	1[illegible]	0	
Leaking or ruptured	10	1	Cardiac arrest at start of operation for rupture of massive aneurysm restarted but death at conclusion of operation, recent myocardial infarct
		1	5th postop day bronchopneumonia
		1	8th postop day pulmonary embolus
		2	2nd postop week renal failure
Occlusion of abdominal aorta and iliac arteries —replacement with homograft or plastic prosthesis	15 (19 ops)	1	1 hr postop coronary thrombosis
		1	24 hr postop cerebral thrombosis
		1	10th postop day pulmonary embolus
		1	2nd postop week intractable ileus
Occlusion of abdominal aorta and iliac arteries —thromboendarterectomy	18	0	In 1 patient with gangrene of bilateral amputation stumps and of penis operation was attempted but abandoned because no patent peripheral vascular bed could be found died 10 days later
Femoropopliteal occlusion (all procedures)	45 (61 ops.)	0	

the survival of half our cases It was noteworthy that 3 patients with ruptured aneurysms had no premonitory symptoms We have found the operation for resection of abdominal aortic aneurysms so satisfactory that it seems justifiable to urge the patient to undergo it if the aneurysm causes pain and to recommend operation even if symptoms are slight or absent.

As regards the operative technique, we believe the most important points are (1) avoidance of damage to the iliac veins and inferior vena cava, (2) injection of a large volume of dilute heparin into that part of the circulation which is rendered temporarily stagnant during operation, (3) excluding the presence of clot in the iliac arteries, (4) proceeding with the operation expeditiously It is important that a patient with a ruptured aneurysm should be taken direct from the ambulance to the theatre, lengthy attempts at resuscitation should not be made elsewhere.

In several of our patients with symptoms of lower-limb ischæmia definite improvement followed removal of the aneurysm, in some, minor emboli had clearly originated from the aneurysm. In considering whether to resect an aortic aneurysm the threat to the lower-limb circulation must be taken into account In 1 case popliteal embolism was the first manifestation of abdominal aneurysm

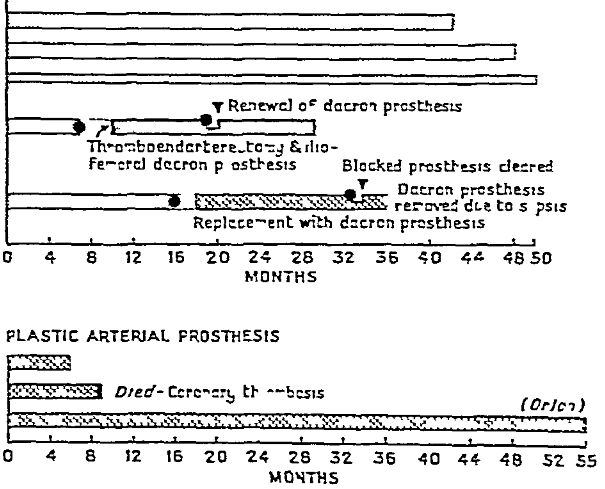
In 1 patient with a leaking aneurysm gangrene developed in a limb after operation and amputation was necessary In retrospect, we consider that this patient, one of the earlier ones in the series, might have been spared this if, at operation, a large volume of heparin solution had been injected into the stagnant circulation inspection for clot had been made at the end, and the operation had been speedily concluded. With greater experience of embolectomy (Tibbs 1960) we would nowadays use this procedure rather than regard it as unduly hazardous as we did in this case Loss of a limb after resection of an aortic aneurysm is possible, but with precautions the risk seems to be small

Occlusion of Aorta and Iliac and Common Femoral Arteries

The information provided by translumbar aortograms was an invaluable guide in operations for occlusion of the abdominal aorta and iliac and common femoral arteries These aortograms, obtained by the methods previously described (Tibbs and Leslie 1958), caused no significant morbidity Translumbar aortography has proved so satisfactory that the radiology department of this hospital does not intend to change over to the more fashionable method of retrograde arterial catheterisation.

In several patients in whom some form of arterial replacement or bypass procedure was carried out for the Leriche type of syndrome, the initial success was short-lived and the " graft " closed off within a few months (see fig 2) Further operations on these occluded " grafts " showed that the original abdominal aortic disease had been more severe than the aortogram indicated, and, where occlusion had developed, the aorta was grossly diseased in the immediately vicinity of the anastomosis Clearly this was inviting spread of atherosclerotic fibrinous occlusion from the diseased aorta into the " graft ", and, incidentally, small emboli (or at any rate blood already beginning to form thrombus) might be carried to the lower limb where they would cause or accelerate arterial occlusion. Anyone who has seen inside such aortæ cannot help being impressed by the loose debris and recent thrombus there, some of this must become detached and travel distally

Surgery of a blocked and atheromatous aorta must be thorough. The aorta can be removed as far as the renal arteries and replaced by a " graft ", this has all the drawbacks of a " graft " already referred to, and, in addition, collaterals are sacrificed. The alternative procedure of thromboendarterectomy is very attractive Our experience (see fig 3) is not very extensive, but abdominal-aortic and common-iliac thromboendarterectomy through a longitudinal incision in the arterial wall has proved a straightforward procedure with a low mortality and morbidity The results in the short period of observation have


HOMOGRAFT

PLASTIC ARTERIAL PROSTHESIS

Fig 2—Progress of patients with occlusion of abdominal aorta and iliac arteries treated by arterial replacement in 1955–59 (for key see fig 1)

The material used for arterial replacement is indicated

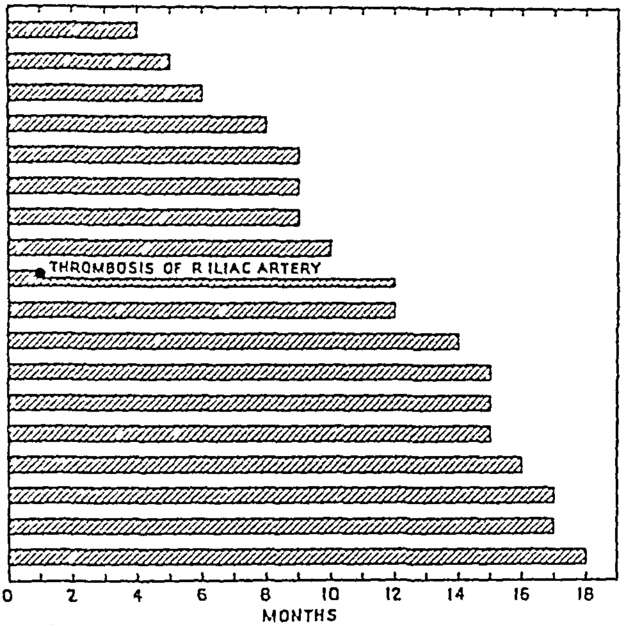


Fig 3—Progress of patients with occlusion of the abdominal aorta and iliac arteries treated by thromboendarterectomy in 1959-60 (for key see fig 1)

Those patients in whom operation also included thromboendarterectomy *on the common femoral artery have not been separately* distinguished

been excellent Thromboendarterectomy was extended to a point above the gross atheroma or about 1 in below the renal arteries, whichever was the lower Commonly the disease process did not stop at this level, and in this event the aorta was manually compressed above the pancreas and the aortic clamp released, then the upper abdominal aorta was cleared of thrombus or loose debris through the opening in the aorta, flushed with heparin solution and a spurt of the patient's own blood, and the clamp reapplied Care was taken not to introduce any material into the renal arteries This manœuvre, performed in about a dozen patients, appeared to provide an excellent compromise

If there was aortographic and arteriographic evidence of significant disease in the lower-limb arterial system, a bilateral lumbar sympathectomy was performed in addition to thromboendarterectomy This operation is not difficult to combine with the other procedure, and we consider it beneficial

Thromboendarterectomy of the external iliac arteries, although technically more difficult, was nevertheless a practical proposition, a ring stripper (Cannon 1958) could usually be passed from the common femoral artery into the common iliac artery

One pattern of arterial occlusion we find of particular interest in this condition the patient has aorto-iliac occlusion or narrowing, and bilateral superficial femoral * blockage, the patency of the common femoral arteries is maintained by collateral flow through the internal and external iliac or the inferior epigastric and the profunda femoris arteries This was observed in 8 cases At operation the aorta and iliac arteries were reopened to restore a pulsatile circulation via the common femoral artery to the profunda femoris, and bilateral sympathectomy was carried out These patients lost all their gluteal claudication and in 7 claudication in the calf became slight or absent, in some, good peripheral pulses were restored although, of course, the superficial femoral arteries remained shut The presence of the extensive collaterals in the thigh necessary for this seem a feature of this particular combination of occlusions Whatever the explanation, in aortoiliac occlusion with bilateral superficial femoral block a good result is usually obtained by *restoring the circulation to the profunda femoris vessels* This needs stressing because over-extensive operations on the arterial tree can only defeat their own ends

Although the indications for reopening completely occluded aortæ or iliac arteries are usually clear, the wisdom of performing thromboendarterectomy on patent but narrowed aortæ and iliac arteries is less certain Narrowing at the aortic bifurcation can cause disabling claudication, although the femoral pulses may appear reasonably strong Our group includes 7 such patients, all of whom did well and were relieved of symptoms If the symptoms are sufficiently severe, such patients can be safely and reliably *relieved by thromboendarterectomy* just like those with complete aortic or iliac artery closure

4 of our patients with occlusion of the aorta and iliac arteries had had this for five years or longer, the onset having occurred at an early age when Buerger's disease had been diagnosed Recent deterioration brought them to the outpatient department, and it seems likely that the correct diagnosis throughout was occlusion or narrowing of the aortic bifurcation Operation transformed all these patients' lives by removing a serious and longstanding disability, and in 2 patients who had already lost a limb imminent danger to the remaining limb was averted In the past, aortic occlusion in young men has clearly been confused with Buerger's disease, in such cases aortography should be performed if there is doubt about the state of the aortic bifurcation

In addition, 5 patients were seen with critically ischæmic lower limbs, and in 3 of these extensive gangrene of a limb was already present Reopening the aorta and iliac arteries produced a dramatic change not only in the limb circulation but also in the patients' general health and well-being Threatened gangrene of the lower extremities in the presence of disease at the aortic bifurcation can almost certainly be reversed provided there is a vascular bed into which the renewed circulation can flow in our series this was achieved in every case but 1 Because surgery is so effective in this condition, this should be widely known so that the condition is diagnosed early and treated surgically before the damage is irretrievable

Femoropopliteal-artery Occlusion

In most patients operated on for occlusion of the superficial femoral artery a homograft or dacron prosthesis bypass was used The "graft" ran from the common femoral artery to either the upper or the lower part of the popliteal artery, which was exposed from the medial aspect The patients have been divided into two groups, those with claudication alone and those with rest pain or gangrene of the toes as well (fig 4)

Good results were obtained in the group with claudication alone, and it is reasonable to infer that in these patients the dacron bypass procedure will give a high proportion of successes which will last for a long period

In the group with rest pain or gangrene, on the c hand, immediate or early closure was common In many of these patients an arterial bypass procedure was used in an attempt to avert amputation, but the majority came to amputation within a few months, often despite repeated attempts to re-establish the circulation (fig 4) A likely explanation is that a lower limb with rest pain in the foot or with actual gangrene almost certainly has two sites of arterial occlusion, the upper being usually in the femoropopliteal region and the lower involving one or both tibial arteries This has repeatedly been demonstrated arteriographically In these circumstances a bypass "graft" inserted into the popliteal artery (it is rarely practicable to anastomose to an artery at a lower level) delivers the blood it carries into a restricted and diseased arterial bed and cannot be expected to succeed for long We have now reluctantly stopped using femoropopliteal bypass "grafts" when the patient complains of rest pain or gangrene, unless a properly timed arteriogram shows a reasonably healthy popliteal artery running into at least one good tibial artery, and even then we often consider it wise to try the other available measures, including sympathectomy, before resorting to a bypass procedure

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* The division of the femoral artery into common femoral above the profunda femoris and a superficial femoral distally is fully justified by functional and pathological considerations It is a shortcoming of modern anatomical terminology that this distinction is not made although in an analogous situation the terms common carotid and common iliac are used moreover the term arteria profunda femoris implies such a distinction

When threatened gangrene is due to occlusion of the limb vessels, arterial surgery is far less likely to succeed than it is when the cause lies in the abdominal arteries

Indications, besides rest pain and gangrene, of likely failure of a bypass "graft" procedure are (1) the appearance on the arteriogram of extensive roughening of the lower parts of the popliteal or the tibial arteries, (2) the absence at operation of the normal polished appearance of the interior of the popliteal artery, and (3) a sense of resistance when the distal vascular bed is flushed through with a syringe All these signs were associated with a high rate of immediate or early closure of the "graft" Often more than one of these adverse features was present in a single case. Once the popliteal artery has actually been opened it is naturally difficult to abandon the procedure, because the arteriotomy, however carefully closed, may cause thrombosis of the meagre stream of blood within But if a roughened interior is found, and if flushing distally offers appreciable resistance, it is probably wisest to turn back and perform sympathectomy if this has not already been done, or even an amputation (if indicated) It is clearly desirable to avoid this situation, and with increased experience we now rely considerably on the arteriogram for recognising the bad proposition in which operation on the arteries should not be attempted, this is particularly important if there is no indication for immediate amputation, because any interference with the popliteal artery may reduce the circulation sufficiently to precipitate intractable rest pain

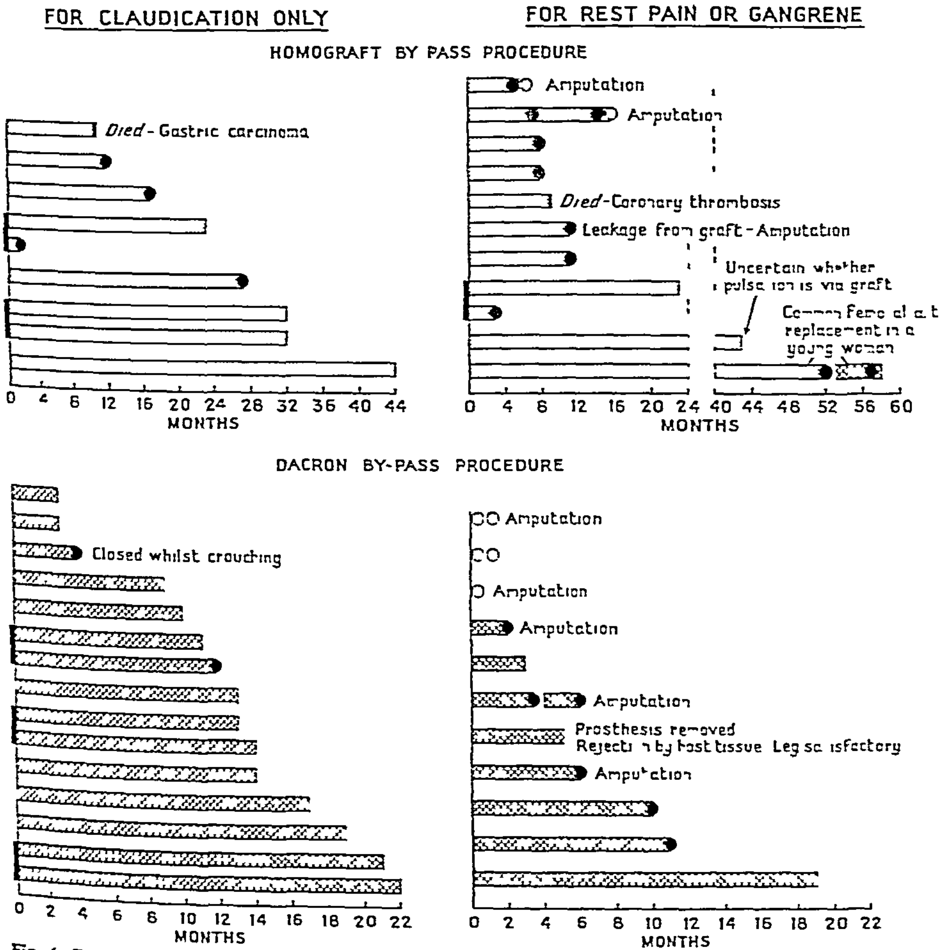


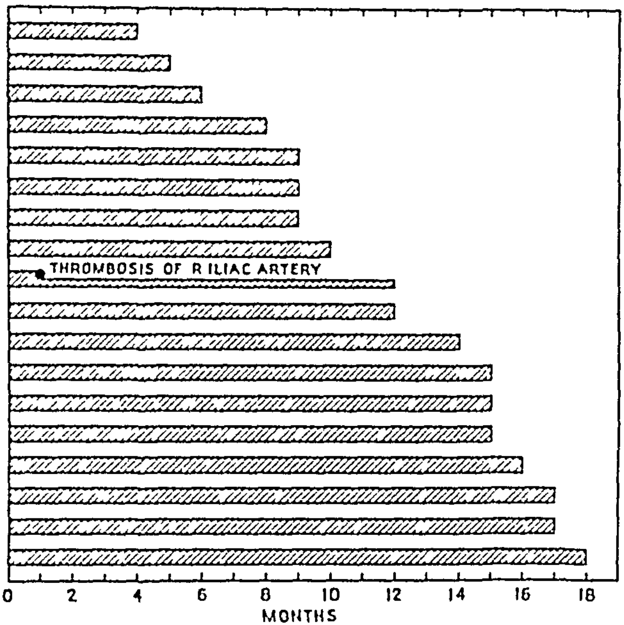
Fig 4—Progress of patients with occlusion of superficial femoral and popliteal arteries treated by arterial bypass procedure in the period 1956–60 (for key see fig 1)

The patients have been divided into two groups according to whether claudication was the only manifestation or whether, in addition, rest pain or gangrene of the toes was present Indication is given if amputation had to be resorted to eventually (Note the different scales employed for homografts and the more recent dacron [terylene] "grafts")

Thromboendarterectomy of Common and Superficial Femoral and of Popliteal Arteries

In 12 patients thromboendarterectomy of the common femoral artery was undertaken in conjunction with a femoropopliteal bypass when gross intimal thickening was apparent, and we believe that a much more satisfactory state of affairs was established in the artery adjacent to the upper end of the "graft", the results in these patients support this conclusion

In only 1 patient out of 6 on whom superficial-femoral-artery thromboendarterectomy was performed were the vessels still open at the end of seven months, in 3 of the cases closure occurred within a few hours and a dacron bypass "graft" was immediately substituted Thus thromboendarterectomy in the superficial femoral artery has not given encouraging results among our few cases In view of the



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In addition, 5 patients were seen with critically ischæmic lower limbs, and in 3 of these extensive gangrene of a limb was already present. Reopening the aorta and iliac arteries produced a dramatic change not only in the limb circulation but also in the patients' general health and well-being. Threatened gangrene of the lower extremities in the presence of disease at the aortic bifurcation can almost certainly be reversed provided there is a vascular bed into which the renewed circulation can flow. In our series this was achieved in every case but 1. Because surgery is so effective in this condition, this should be widely known so that the condition is diagnosed early and treated surgically before the damage is irretrievable.

Femoropopliteal-artery Occlusion

In most patients operated on for occlusion of the superficial femoral artery a homograft or dacron prosthesis bypass was used. The "graft" ran from the common femoral artery to either the upper or the lower part of the popliteal artery, which was exposed from the medial aspect. The patients have been divided into two groups, those with claudication alone and those with rest pain or gangrene of the toes as well (fig 1).

Good results were obtained in the group with claudication alone, and it is reasonable to infer that in these patients the dacron bypass procedure will give a high proportion of successes which will last for a long period.

In the group with rest pain or gangrene, on the c hand, immediate or early closure was common In many of these patients an arterial bypass procedure was used in an attempt to avert amputation, but the majority came to amputation within a few months, often despite repeated attempts to re-establish the circulation (fig 4) A likely explanation is that a lower limb with rest pain in the foot or with actual gangrene almost certainly has two sites of arterial occlusion, the upper being usually in the femoropopliteal region and the lower involving one or both tibial arteries This has repeatedly been demonstrated arteriographically In these circumstances a bypass " graft " inserted into the popliteal artery (it is rarely practicable to anastomose to an artery at a lower level) delivers the blood it carries into a restricted and diseased arterial bed and cannot be expected to succeed for long We have now reluctantly stopped using femoropopliteal bypass " grafts " when the patient complains of rest pain or gangrene, unless a properly timed arteriogram shows a reasonably healthy popliteal artery running into at least one good tibial artery, and even then we often consider it wise to try the other available measures, including sympathectomy, before resorting to a bypass procedure

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* The division of the femoral artery into common femoral above the profunda femoris and a superficial femoral distally is fully justified by functional and pathological considerations. It is a shortcoming of modern anatomical terminology that this distinction is not made, although in an analogous situation the terms "common carotid" and "common iliac" are used; moreover the term "arteria profunda femoris" implies such a distinction.

When threatened gangrene is due to occlusion of the limb vessels, arterial surgery is far less likely to succeed than it is when the cause lies in the abdominal arteries

Indications, besides rest pain and gangrene, of likely failure of a bypass " graft " procedure are (1) the appearance on the arteriogram of extensive roughening of the lower parts of the popliteal or the tibial arteries, (2) the absence at operation of the normal polished appearance of the interior of the popliteal artery, and (3) a sense of resistance when the distal vascular bed is flushed through with a syringe All these signs were associated with a high rate of immediate or early closure of the " graft " Often more than one of these adverse features was present in a single case Once the popliteal artery has actually been opened it is naturally difficult to abandon the procedure, because the arteriotomy, however carefully closed, may cause thrombosis of the meagre stream of blood within But if a roughened interior is found, and if flushing distally offers appreciable resistance, it is probably wisest to turn back and perform sympathectomy if this has not already been done, or even an amputation (if indicated) It is clearly desirable to avoid this situation, and with increased experience we now rely considerably on the arteriogram for recognising the bad proposition in which operation on the arteries should not be attempted, this is particularly important if there is no indication for immediate amputation, because any interference with the popliteal artery may reduce the circulation sufficiently to precipitate intractable rest pain

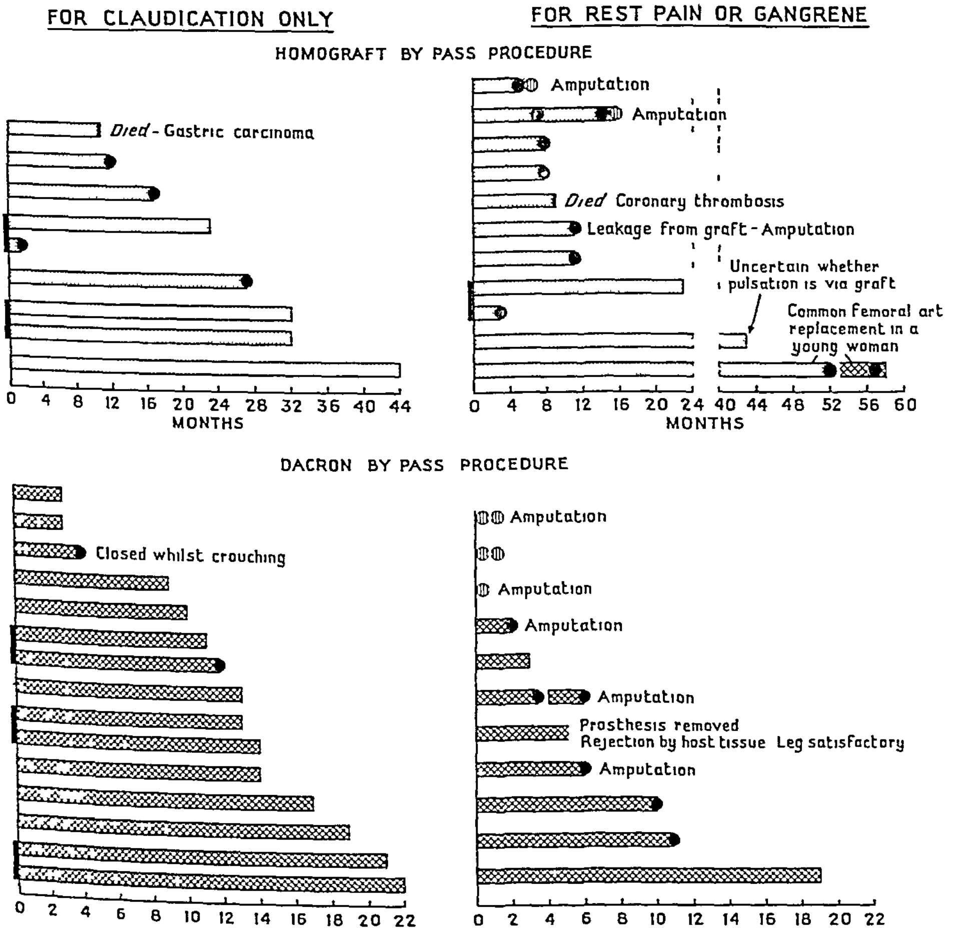

Fig 4—Progress of patients with occlusion of superficial femoral and popliteal arteries treated by arterial bypass procedure in the period 1956–60 (for key see fig 1)

The patients have been divided into two groups according to whether claudication was the only manifestation or whether, in addition, rest pain or gangrene of the toes was present Indication is given if amputation had to be resorted to eventually (Note the different scales employed for homografts and the more recent dacron [terylene] ' grafts ')

Thromboendarterectomy of Common and Superficial Femoral and of Popliteal Arteries

In 12 patients thromboendarterectomy of the common femoral artery was undertaken in conjunction with a femoropopliteal bypass when gross intimal thickening was apparent, and we believe that a much more satisfactory state of affairs was established in the artery adjacent to the upper end of the " graft ", the results in these patients support this conclusion

In only 1 patient out of 6 on whom superficial-femoral-artery thromboendarterectomy was performed were the vessels still open at the end of seven months, in 3 of the cases closure occurred within a few hours and a dacron bypass " graft " was immediately substituted Thus thromboendarterectomy in the superficial femoral artery has not given encouraging results among our few excellent results obtainable in the abdominal arteries, it seems possible that an important factor in the relatively poor results may be the use of a blind technique (i.e., a ring stripper) on the lower-limb arteries, combined with the difference in the size of the lumen. At this stage in our experience we conclude that thromboendarterectomy on common femoral arteries or arteries proximal to them has proved successful, but below this level the procedure has been disappointing, but we have recently seen the good results being obtained by Prof. C. Semb and his colleagues in Oslo and remain interested in the method.

Operative Mortality

Failures to save the lives of patients with ruptured aneurysms are not considered in this paper. Apart from the deaths already discussed to which shortcomings or infections of the material used for arterial replacement contributed, there were 4 deaths in hospital precipitated in some way by the operation (table III). 3 deaths were due to thrombotic conditions—coronary thrombosis, cerebral thrombosis, and pulmonary embolism. The patients operated on would undoubtedly be more liable to these complications; because of this, efforts were made to avoid anoxia or hypotension during operation, and all patients were urged to move their legs freely after operation to discourage venous thrombosis. These deaths occurred early in the series, and possibly the risk of these complications has been reduced, but the risk remains in any procedure on a patient with advanced vascular disease. 1 patient died of intractable ileus, the cause of which remained obscure despite re-exploration (permission for necropsy was not given). Since this episode, in abdominal procedures we have routinely delivered all the small bowel and wrapped it in moist towels; at the end of the operation it is carefully returned into an " ideal " anatomical disposition. A gastric suction tube and intravenous drip are employed postoperatively until flatus is passed and bowel sounds are satisfactory; continuous suction is always applied if the abdomen becomes distended. With this routine, in about 50 patients no alarming ileus has been observed, although in 2 small-bowel obstruction developed owing to adhesions and required further operation.

Treatment of the Causal Disease—Atherosclerosis

The surgeon dealing with such cases as those described here is merely putting right the most obvious expression of the generalised state of atherosclerosis. Progressive atherosclerosis not only will jeopardise the " graft " but also may involve the opposite limb or disable the patient by coronary thrombosis.

Most of our patients operated on for occlusive disease were given long-term anticoagulant therapy. It is obviously difficult to obtain convincing evidence on the value of this therapy; as the results show, it does not provide complete protection from graft closure or further expressions of atherosclerosis, but it may provide some measure of protection. The evidence requires further study and we hope to analyse our experience later.

Obese patients were urged to follow a weight-reducing diet; in patients with occlusion of the abdominal arteries, we often insisted on this before undertaking surgery, partly to facilitate the operation (a very real advantage) and partly because we considered obesity highly disadvantageous to the atherosclerotic patient. The patients were encouraged to take regular exercise before and after operation because physical inactivity was thought to be another adverse factor; smoking, although not forbidden, was discouraged. A diet of unsaturated fats was not imposed on the patients, but they were advised to avoid eating large quantities of fat. As with anticoagulants, it is impossible to assess the value of these measures. Without doubt weight reduction was of value to the patients, and many expressed relief at the improvement in their general well-being after losing one or two stone in weight. The advantages of driving a bargain with the patient to do the operation after he had lost weight were quite obvious.

Summary

Five years' experience of operations for arterial replacement and reconstruction on account of aneurysm or occlusive disease of arteries is reviewed.

Evidence is given that homografts lack durability and should usually be avoided. Arterial prostheses of crimped ' Dacron ' (' Terylene ') proved very satisfactory and apparently more durable.

Disastrous results may follow infection of any form of arterial prosthesis, and thus reconstruction of the patient's own arteries, whenever this is feasible, is to be preferred.

Replacement of abdominal aortic aneurysms by a homograft and plastic prosthesis proved satisfactory. Of patients with a leaking abdominal aortic aneurysm who reach the operating-theatre alive, about half survive, and the survivors may remain well for some years.

Abdominal-aortic and iliac-artery occlusion or narrowing responds well to thromboendarterectomy. Good results can be obtained by restoring a pulsatile flow in the profunda femoris even if the superficial femoral arteries are closed. In younger patients aortic occlusion may be misdiagnosed as Buerger's disease. In the presence of aortic or iliac-artery occlusion, impending gangrene of the lower extremities can be consistently relieved by reopening these vessels.

In occlusion of the superficial femoral or popliteal arteries, bypass " grafting " gives good results over long periods in patients with simple claudication. When rest pain or actual gangrene is present the benefit tends to be short-lived and it is often not possible to avert amputation.

Thromboendarterectomy is satisfactory in the common femoral artery or in the major abdominal arteries, but in the superficial femoral and popliteal arteries thromboendarterectomy using a ring stripper is usually less successful.

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BRONCHODILATORS AND CORTICOSTEROIDS IN ASTHMA

Forced Expiratory Volume as an Aid to Diagnosis and Treatment

K. M. HUME
M.D. Lond.
ASSISTANT MEDICAL OFFICER

E. RHYS JONES
M.B., B.Sc. Wales, M.R.C.P.
FIRST ASSISTANT MEDICAL OFFICER

KING EDWARD VII SANATORIUM, MIDHURST, SUSSEX

SPIROMETRIC investigation is now used in many chest units to determine whether wheezing and dyspnœa are due to the remediable condition, reversible bronchospasm, or to permanent bronchial narrowing, which will not respond to bronchodilator therapy, associated with diseases such as emphysema or fibrosis of the lung. The usual test is the forced vital capacity, which is a single forced expiration recorded with a spirometer (Bernstein et al. 1952), and the initial part of the expiration, commonly the volume expired in the first second (the forced expiratory volume in one second, F.E.V.$_{1\cdot0}$), is a more reliable index than the value for the total expiration. When bronchial narrowing is present the value obtained decreases, and if, after administering a bronchodilator, this increases, it can be deduced that the bronchodilator is effective.

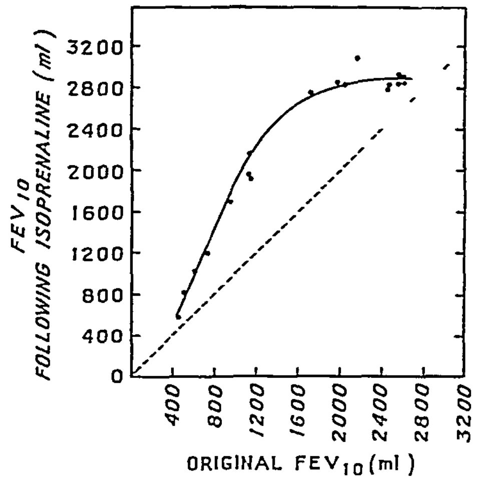
By repeating these tests daily we obtained different response patterns in asthma and in the other diseases which may cause wheezing, and even in the various forms of asthma itself. Here we report the method of investigating wheezing and also how, by daily tests, the best way to use bronchodilator and corticosteroid therapy can be determined. The results of two trials (Hume and Gandevia 1957, Hume and Rhys Jones 1960) will serve to illustrate how this method can be applied in the clinical management of patients. In both trials the F.E.V.$_{1\cdot0}$ was measured daily in patients from the time they were admitted to hospital in status asthmaticus until they had completely recovered.

Recording of F.E.V.$_{1\cdot0}$

Before and after Inhaled 1% Isoprenaline

Complete readings for one patient are shown in fig. 1, the daily initial F.E.V.$_{1\cdot0}$ is plotted against the F.E.V.$_{1\cdot0}$ after administering 1% isoprenaline as aerosol.

When intrinsic asthma was very severe, as indicated by low initial F.E.V.$_{1\cdot0}$ values, little improvement followed inhalation of isoprenaline. As the asthma responded to treatment over the ensuing days and the pre-inhalation F.E.V.$_{1\cdot0}$ rose, so the improvement resulting from the inhalation of isoprenaline increased until the maximum response for that patient was obtained when all bronchial constriction was reversed. Thereafter the pre-inhalation F.E.V.$_{1\cdot0}$ approached the now constant post-inhalation value. The curve for fig. 2 (patient A) shows the same results plotted in a more useful way with the figure for the pre-inhalation or initial F.E.V.$_{1\cdot0}$ subtracted from the post-inhalation value so that the ordinate measures the improvement resulting from the inhalation of isoprenaline.



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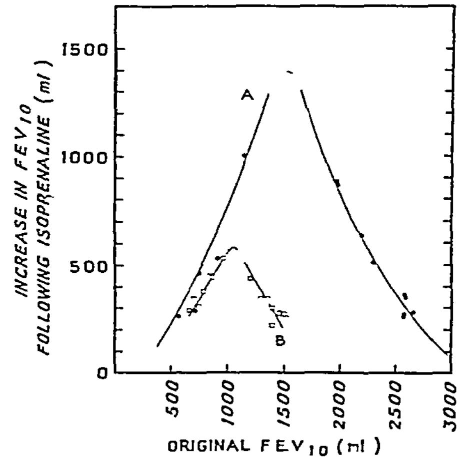
The maximum response to a bronchodilator, though limited when asthma was severe, was reached with a low dosage, but if a second bronchodilator with a different pharmacological action was then administered, the F.E.V.$_{1\cdot0}$ improved further. The order in which the drugs were



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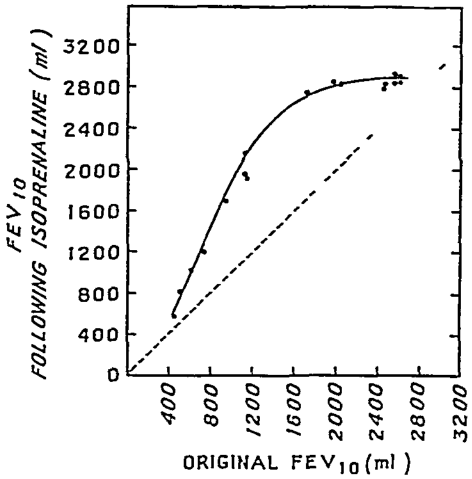

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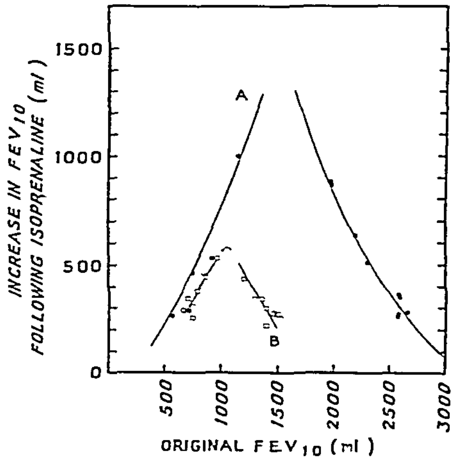

Fig 2—Data of fig 1 plotted with improvement in the forced expiratory volume in first second as ordinate

Patient A is the one with intrinsic asthma in Fig 1 Patient B shows the nature of the response when intrinsic asthma coexists with emphysema given affected the response, thus intravenous aminophylline after 1% isoprenaline as aerosol was generally more effective than when the drugs were administered in the reverse order

Diagnosis

Recurrent attacks of wheezing in adults may be due to intrinsic or extrinsic asthma Clinical differentiation is often possible, intrinsic asthma characteristically appears for the first time in adult life in the absence of demonstrable allergens in the environment outside the body, and the attacks become progressively longer and more frequent until, within a few years, the patient is rarely free from chronic wheezing upon which acute attacks of status asthmaticus, responding poorly to bronchodilators, are superimposed Extrinsic asthma, on the other hand, frequently appears in childhood and is triggered off by external allergens, and the attacks, although acute, are often short, commonly responding dramatically to bronchodilator therapy But the nature of the asthma may vary and the extrinsic form may change into the intrinsic when the patient reaches adult life Clinical diagnosis is further complicated because the forms are not entirely age-specific and, particularly in intrinsic asthma, also because of coexisting emphysema The presence of emphysema can often only be confirmed after the asthma has completely resolved, which necessitates postponing prognosis

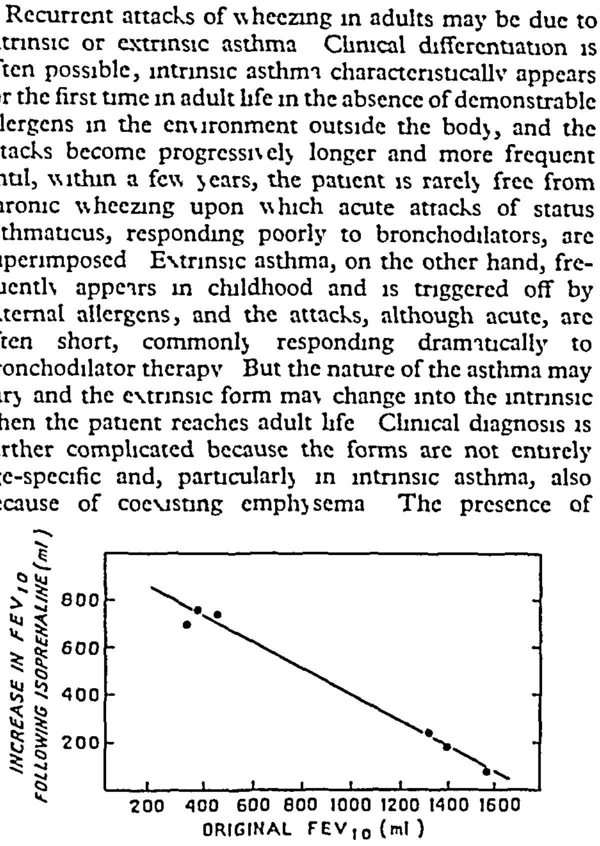

Fig 3—Response to aerosol isoprenaline of a patient with extrinsic asthma

In contrast to the patients with intrinsic asthma shown in fig 2 there is a linear response

By plotting the response to inhaled 1% isoprenaline it is possible to differentiate between the various conditions before recovery has taken place Four types are recognisable

Type 1—This corresponds to the clinical group of intrinsic asthma without associated emphysema and has already been illustrated (patient A, fig 2)

Type 2—This is found in patients with uncomplicated extrinsic asthma in whom the bronchodilator effect is maximal even when the F.E.V.$_{1\cdot0}$ is low The results in this type of asthma are shown in fig 3 It was not possible to test the patient over a wide initial-F.E.V.$_{1\cdot0}$ range because complete recovery followed the administration of isoprenaline The three left-hand tests where the original F.E.V.$_{1\cdot0}$ was low were performed during three separate attacks of asthma In each case the test next day showed that the effect of the isoprenaline had been maintained and hardly any bronchospasm was present

The patient, a woman aged 23, had had short-lived acute attacks of asthma since childhood Although external allergens could not be identified, her attacks were readily triggered off by colds and emotional upsets, and the nature of the attacks, which responded rapidly and completely to bronchodilators, conformed to the pattern of extrinsic asthma

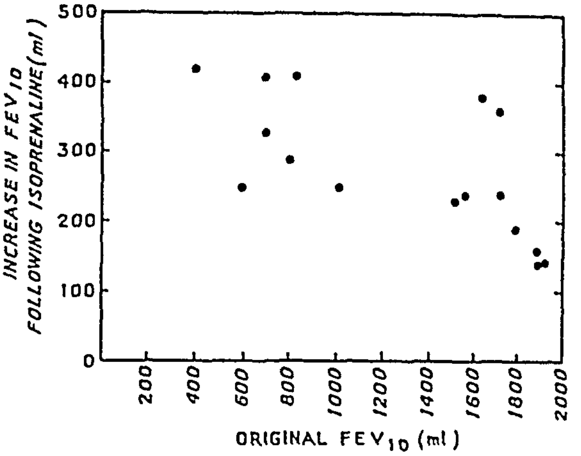

Fig 4—An intermediate response in a patient in the transitional phase between extrinsic and intrinsic asthma

Type 3—Only two patients fell into this category, but the clinical history suggested that it may be a separate entity of particular interest, representing the change-over from extrinsic to intrinsic asthma The results for one of the patients are shown in fig 4 There was an incomplete response, intermediate between those in types 1 and 2, to the bronchodilator when the original F.E.V.$_{1\cdot0}$ was low When the original F.E.V.$_{1\cdot0}$ exceeded about 1600 ml the response was the same as in patient A (fig 2), as might have been expected when the full bronchodilator response was reached

Both patients were young men, aged 20 and 28, who had had typical attacks of extrinsic asthma since childhood, which had recently changed in character, the attacks becoming more long drawn-out and resistant to bronchodilator therapy

Type 4—Coexistent emphysema is disclosed by one of two types of response, according to whether asthma with emphysema, or emphysema with reversible bronchial construction, predominates Patient B (fig 2) exemplifies the first of these two groups of cases

This patient, a woman aged 45, had had attacks of asthma for 40 years, which had over the past 10 years, during which she had attended this hospital, been intrinsic in nature She had clinical and radiological evidence of advanced emphysema

The results have been included in fig 2 for comparison with those in patient A with uncomplicated intrinsic asthma The peak of the response curve is considerably lower in patient B, and extrapolation of the right-hand limb to the abscissa gives a maximum F.E.V.$_{1\cdot0}$ for the patient of 1700 ml, whereas the predicted normal value is 2[illegible]00 ml

When emphysema is the primary disease, and reversible bronchial constriction secondary, the results do not follow any particular pattern and changes [illegible] distributed haphazardly

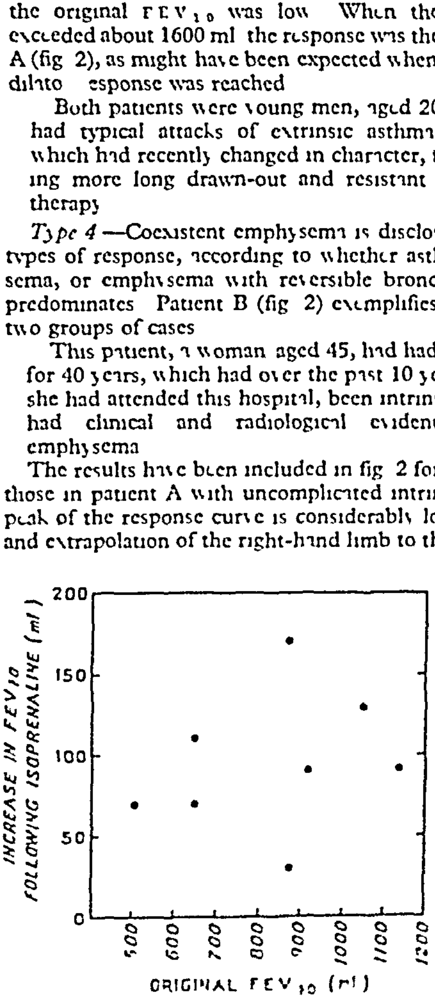

Fig 5—Case of emphysema with bronchospasm showing haphazard distribution of points Note [illegible] scale

as is shown in fig. 5, so that no curve can be fitted to them. Why the response to bronchodilators is so variable and unpredictable is not clear, but we feel it may be due to other mechanical factors resulting from the emphysema.

In these cases patients with asthma can be distinguished from those with asthma and emphysema by expressing the F E V$_{1\cdot 0}$ as a percentage of the vital capacity (Thomson and Hugh-Jones 1958).

Treatment

Intrinsic asthma with status asthmaticus is usually treated at first with bronchodilator drugs and antibiotics, corticosteroids being withheld while the effect of this treatment is observed (Medical Research Council 1956). When the attack has been precipitated by a factor, such as a fresh infection, which can be overcome by appropriate antibiotics, this treatment may tide the patient over the relapse. Frequently, however, clinical improvement is slow and the result disappointing and then corticosteroid therapy must be considered.

Corticosteroids are valuable in the treatment of intrinsic asthma, both in acute status asthmaticus and also for maintenance therapy in cases which will otherwise relapse when treatment is withdrawn. Indications for corticosteroid therapy should be clearly defined because even the latest corticosteroids have serious side-effects limiting their use. Clinical assessment of a case presents many difficulties. The natural course of the disease is very variable, both in different cases and in the different phases in any one patient. Factors such as infection, reversible bronchial constriction, and irreversible changes in the bronchi and lung parenchyma all contribute to the clinical manifestations. Each has to be considered in relation to the duration, frequency, and severity of the asthmatic attacks, and no single factor provides a satisfactory clinical yardstick to determine the need for steroids.

The most obvious requirement is a diagnostic method to distinguish cases which will respond to bronchodilators from those which require corticosteroids. Coexisting emphysema must also be detected; this adversely affects the prognosis and makes it even more important to control any bronchial obstruction in order to avoid progressive emphysematous change. Accurate diagnosis can be achieved with the daily F E V$_{1\cdot 0}$ tests; over the past four years we have used this method, together with clinical criteria, to decide on the treatment of severe asthma.

When a patient is admitted, a clinical assessment is made. If the attack is very severe and the asthma must be relieved at once, corticosteroid therapy with corticotrophin drip is started immediately. If the patient's life is clearly not in immediate danger, energetic bronchodilator therapy with 1% isoprenaline as aerosol and intravenous aminophylline is begun. The F E V$_{1\cdot 0}$ before and after inhaled isoprenaline is first measured as soon as practicable, with regard to the fact that when wheezing is very severe the patient must rest and the expiratory effort necessary to perform the F E V$_{1\cdot 0}$ may be exhausting and may even temporarily increase the wheezing (Hume 1959). The optimum bronchodilator effect results from administering relatively small doses of the drugs—in the case of isoprenaline the inhalation of a 1% solution for thirty seconds, and in the case of aminophylline an intravenous injection of 0·25 g (Hume and Rhys Jones 1960). In these low doses these drugs can exert their maximum therapeutic effect without causing side-effects. Furthermore, the trial demonstrated that, when the initial F E V$_{1\cdot 0}$ is low, although the maximum effect of any one bronchodilator may be clinically undetectable, tests will show that improvement has occurred. A greater improvement was observed when two or more bronchodilator drugs of different pharmacological groups were employed. The order in which the drugs were given was important: sympathomimetic drugs such as isoprenaline should be given before the parasympathetic-blocking atropine, or aminophylline.

The F E V$_{1\cdot 0}$ tests are repeated daily during bronchodilator therapy; some patients make steady progress and ultimately recover. But if after a week there is no improvement in the daily initial F E V$_{1\cdot 0}$ value, and the patient remains in status asthmaticus, corticosteroid therapy is commenced, with 30 mg. of prednisone daily: rapid improvement, as shown by the daily F E V$_{1\cdot 0}$ figure, is almost invariable. The bronchodilator drugs become more effective, and the patient's response resembles that of patients A and B (fig. 2). When the patient's response has passed the peak of the curve and lies on the descending limb, and bronchodilator effect is maximal, the corticosteroid is gradually reduced but bronchodilator therapy is maintained. Daily F E V$_{1\cdot 0}$ tests will show any decrease in the value as the corticosteroid is withdrawn. Complete withdrawal is possible in some patients; their response remains to the right of the peak of the curve—i.e., they remain fully responsive to bronchodilators. But in the majority of patients the daily F E V$_{1\cdot 0}$ decreases in value and the response once again approaches the peak of the curve and reverses down the left-hand limb. These patients require bronchodilator therapy combined with corticosteroids for maintenance.

Observations on patients after relapse, while either they were receiving a reduced dose of corticosteroid or after the drug had been completely withdrawn, showed that adjusting the treatment caused the test results to follow the response curve originally plotted.

We have tested patients within a few hours of relapse, when the response lies to the left of the peak of the curve. The effect in these cases has been greater than expected; the isoprenaline was still apparently exerting a maximum effect, and the patient with intrinsic asthma was responding like one with extrinsic asthma. But this maximal response lasted only 48 hours, and if corticosteroid dosage was not adjusted the improvement after inhaled isoprenaline reverted to the level of the left-hand limb of the original curve.

This observation suggested that there was a "latent period" of about 48 hours before changes in the bronchial muscle resulted in a recurrence of the "drug-fast state". It also underlined the importance of observing patients closely, and performing daily tests, while corticosteroid dosage was being reduced.

Patients were not deeply aware of respiratory disability when the value of the F E V$_{1\cdot 0}$ was at the level associated with maximum isoprenaline response (the peak of the curve) (Hume and Gandevia 1957). We agree that a satisfactory way to determine the minimum corticosteroid dosage for maintenance is to maintain the value of the F E V$_{1\cdot 0}$ on the right-hand limb of the curve near the peak rather than attempt to achieve an asthma-free state. At this F E V$_{1\cdot 0}$ level the patients remained fully responsive to bronchodilators on the minimum maintenance dosage of corticosteroids.

From the response curve for a patient with intrinsic asthma requiring maintenance corticosteroids and bronchodilators, we can rapidly determine which group of drugs to increase in dosage when relapse threatens If the F E V$_{1\,0}$ decreased and the value lay on the left-hand limb (and full bronchodilator response was not obtained), we found that the patient was liable to develop status asthmaticus unless the corticosteroid dosage was increased But if the figure for F E V$_{1\,0}$ lay at the peak or to the right of it, then increasing the dosage of bronchodilators was usually enough to prevent severe asthma

Of the two patients whose response resembled the pattern shown in fig 3, one required corticosteroids both in attacks of status asthmaticus and for maintenance, while the other responded to antibiotics and bronchodilators alone The patient requiring corticosteroids was picked out by testing as above

The treatment of patients with emphysema and reversible bronchospasm (fig 4) is not the same as of those we have discussed in whom, although some emphysema may coexist, asthma is the major disability

As a rule, the primarily emphysematous patients respond to bronchodilator therapy, but even when bronchospasm is relieved they may still have incapacitating dyspnœa due to irreversible changes in the lung parenchyma and bronchi But some do not respond satisfactorily to bronchodilators, apparently as a result of producing excess of mucoid or mucopurulent sputum Appreciable improvement in these patients can be obtained with corticosteroids, since these reduce the amount of sputum Withdrawal of corticosteroids will have to be carried out over longer periods in these patients, in whom, possibly because of their high average age, the adrenals appear unable to function again, this must be borne in mind before starting corticosteroid therapy

Summary

Daily measurement of the forced expiratory volume is of value in the diagnosis and treatment of patients with a chronic wheeze due to asthma, emphysema, or both

The forced expiratory volume in the first second (F E V$_{1\,0}$) is more reliable for this purpose than the complete forced vital capacity

Five different patterns of response of diagnostic significance are obtained when 1% isoprenaline is inhaled as an aerosol

F E V$_{1\,0}$ measurements can be used in treatment to determine whether corticosteroids are needed to supplement the bronchodilator drugs

We wish to thank Sir Geoffrey Todd for advice in the preparation of the paper, Boots Ltd for supplies of intravenous aminophylline, and Messrs Allen & Hanburys Ltd for statistical advice

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'There is a very ancient belief that health is a simple state, to be attained by observing a few simple positive and negative rules But it follows from the complexity of the body that health cannot be a simple state Because there are literally thousands of ways of being ill to be well one has to be well in thousands of ways at once Though a healthy person will have neither diphtheria nor diabetes, he will not escape them because he is healthy, but he will be healthy because he has not got them —SIR RUSSELL BRAIN Osler memorial oration to Canadian Medical Association, 1960 *Practitioner*, October, 1960, p 185

RUPTURE OF THE INTERVENTRICULAR SEPTUM ASSOCIATED WITH ACUTE MYOCARDIAL INFARCTION

K F R SCHILLER
M A, B M Oxon, M R C P
MEDICAL REGISTRAR, THE LONDON HOSPITAL, E 1

THE physical signs in a patient who died from rupture of the interventricular septum (I V S) following myocardial infarction were first described by Latham (1845) Although several descriptions of this condition appeared over the next few years—e g, Galt (1909)—Brunn (1923) made the first correct diagnosis during life The first successful operation for ruptured I V S following myocardial infarction was performed by Cooley et al (1957) Perforation of the I V S in association with myocardial infarction is uncommon Sanders et al (1956) could collect only 121 cases, adding 8 of their own Other small series have since appeared—e g, Malone and Parkes (1955) and Swithinbank (1959) Here I describe 7 further cases, in 6 of which the diagnosis was made during life

Case-records

Case 1 —A man, aged 73, was admitted on Feb 25, 1950 Five days before admission he had collapsed with severe chest pain Symptoms eased, but returned on Feb 25

Examination and course —The patient was profoundly shocked, with an impalpable pulse and unrecordable blood-pressure The apex beat was in the anterior axillary line There was a loud precordial systolic murmur Despite emergency treatment, the patient died soon after admission An electrocardiogram (E C G) was not taken

Necropsy

The heart weighed 520 g The left ventricle was hypertrophied A soft yellowish area of recent infarction was found in the posterior and upper thirds of the I V S and in the whole of the posterior wall of the left ventricle There was a vertical rent 4 cm long through the upper part of the I V S at its junction with the posterior wall A recent thrombus occluded the right coronary artery for 1 7 cm before the start of the posterior descending branch Older recanalised thrombi were found in the right and circumflex coronary arteries

Postmortem diagnosis intramuscular rupture of the heart from recent infarction, with fresh thrombus in an atheromatous coronary artery, also old coronary thromboses

Case 2 —A man of 60 was admitted on Jan 1, 1955 Two days before admission, he had had severe retrosternal chest pain radiating to the back and lasting thirty minutes On the day of admission the pain returned after mild exertion

Examination and course —The patient was a plethoric fit looking man in no apparent distress, pulse rate 71, blood pressure 200/115 mm Hg, apex beat diffuse, heart sounds normal, no evidence of shock or congestive cardiac failure E C G (fig 1a) showed a QS pattern in CR$_1$, CR and CR$_4$, with RST elevation in I and all chest leads, and T inversion in II and III He was treated symptomatically for acute myocardial infarction Anticoagulants were not given at this stage Two days later there was a rise in pulse rate and in temperature His condition was then much worse, with cyanosis, blood pressure 120 70, and raised jugular venous pressure A loud systolic murmur over the precordium obscured the heart sounds Crepitations were present over both lung bases Rupture of the I V S was diagnosed and anticoagulant therapy started The blood pressure continued to fall and congestive cardiac failure supervened E C G showed no new changes A day later a systolic thrill became palpable over the precordium On Feb 16 a phonocardiogram (incomplete because of the patient's condition) was recorded, this showed a large systolic murmur with a small gap before the second sound The congestive cardiac failure however, proved intractable, and the patient died on March 15, 1955

Necropsy

The heart weighed 420 g , and both ventricles were slightly dilated The left ventricular wall over the anterior apical portion was thinned to 0 3 cm , with an aneurysmal dilatation A thinned area of old cardiac infarction extended over the anterior 3 cm of the I V S , enclosing a small round-bordered septal defect at the junction of the upper two-thirds and lower third of the septum (fig 2) There was fresh infarction of the left ventricle The left descending coronary artery was occluded by soft brown thrombus for 1 cm about 3 cm from the artery's origin

Postmortem diagnosis defect of I V S from rupture of recently infarcted myocardium, old cardiac infarction

Case 3 —A signalman of 49, with no serious previous illnesses, was admitted on March 22, 1956, complaining of sudden severe epigastric pain associated with nausea and vomiting

Examination and course —The patient was an obese man, in obvious pain His blood-pressure was 140/100 mm Hg, with normal heart sounds and no precordial murmurs On March 26 he had a loud harsh pansystolic murmur loudest over the apex, no thrill was felt The jugular venous pressure was elevated E C G (fig 1b) showed deep Q waves together with definite RST elevation in leads I, II, III, aVF, V_5, and V_6, and flattening of T waves in V_1 A diagnosis of acute cardiac infarction was therefore confirmed, though the significance of the systolic murmur was not appreciated Congestive cardiac failure and attacks of acute left ventricular failure were treated, and the patient was given anticoagulant therapy Later, a precordial thrill was felt, and rupture of the I V S was tentatively suggested The patient never rallied, rhythm changes supervened, and he died on May 27, 1956

Necropsy

The heart, which weighed 514 g , showed right ventricular and left ventricular dilatation The apical two-thirds of the septum was replaced by a thin fibrous scar in the middle of which there was a rent 1 cm long, about 2 cm from the apex The apical third of the rest of the left ventricular wall was extremely thin but not fibrosed A large plaque of atheroma almost obstructed the left main coronary artery 2 cm from its bifurcation

Postmortem diagnosis perforated septal cardiac infarct, with underlying myocardial fibrosis

Case 4 —A woman of 62 was admitted on Dec 19, 1957 On Dec 15 she had had an attack of severe retrosternal pain radiating to the chin, accompanied by nausea and vomiting Acute myocardial infarction was diagnosed, and she was ordered bed rest at home, anticoagulants were not prescribed No systolic murmur was heard On the evening before admission the pain returned, and this persisted to the next morning when her doctor referred her to hospital

Examination and course —On admission the patient was very ill and was mentally confused She was pale and sweating and had a feeble irregular pulse, elevation of jugular venous pressure, and an unrecordable blood-pressure The apex beat was not felt, the heart sounds were faint but there was a loud harsh pansystolic murmur, best heard over the apex, diastole was clear Crepitations were present at the bases of the lungs E C G (fig 1c) showed atrial fibrillation, with deep Q in lead III and elevation of the RST segment

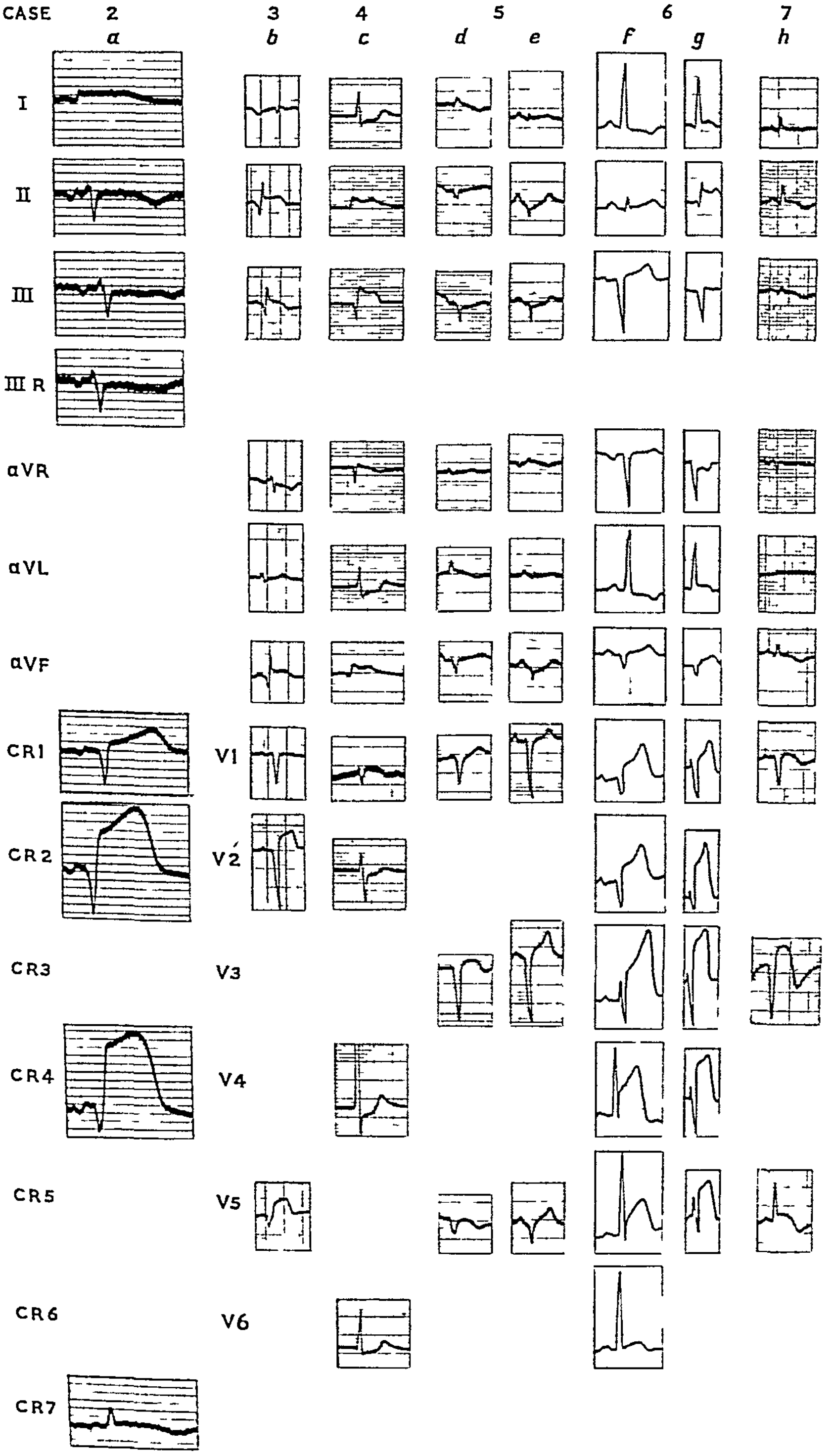

Fig 1—Electrocardiograms from 6 patients with rupture of interventricular septum

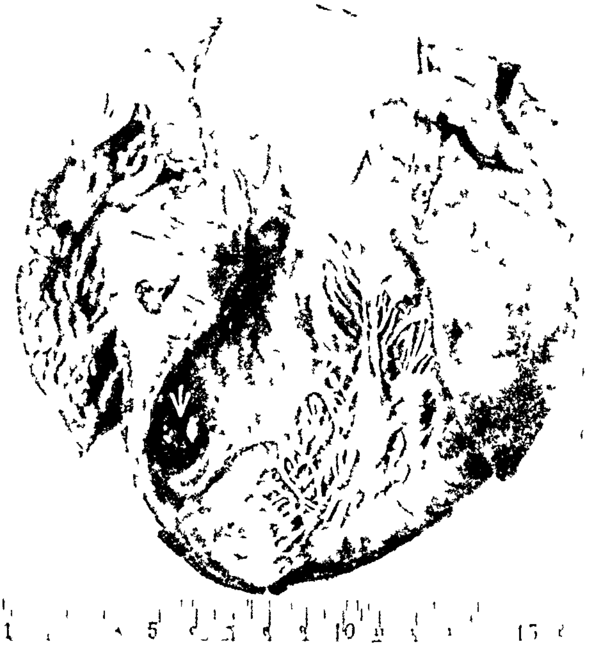

Fig 2—Case 2: heart from left ventricular aspect, showing rupture of interventricular septum of 2 months standing

in leads II, III, and aVF T in V_2 was a little flattened Acute myocardial infarction with perforation of the I V S was diagnosed The patient was treated with intravenous heparin and noradrenaline, without response An E C G the day after admission showed no significant changes The patient died a few hours later

Necropsy

The heart weighed 410 g and showed early left ventricular hypertrophy On the left side of the I V S there was a large ragged area 2 cm in diameter about 3 cm from the apex (fig 3) Despite some organised clot, there was free communication between the two ventricles through this interventricular tear Fresh thrombus was found in the right coronary artery, 0 5 cm from its origin, completely occluding the lumen (fig 4) In addition, there were bilateral pleural effusions and considerable congestion of lungs and liver

Postmortem diagnosis ruptured I V S following acute myocardial infarction due to thrombosis of right coronary artery

Case 5 —A woman of 77 was admitted on July 9, 1958 *For some months she had had exertional chest pain and dyspnœa* On the day of admission she suddenly felt a crushing central chest pain radiating to the left arm, associated with nausea and vomiting

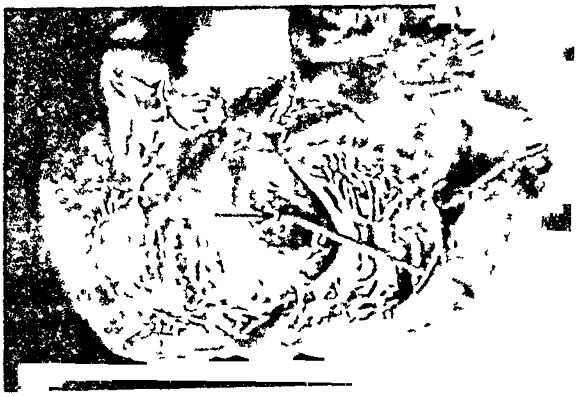

Fig 3—Case 4 heart from left ventricular aspect showing rupture of interventricular septum of 2 days standing

Examination and course —The patient was fully conscious, shocked, and in severe pain Pulse-rate 100 per min , blood pressure 150/100 mm Hg, there was central cyanosis, and jugular venous pressure was increased Crepitations were heard in both lung bases The clinical diagnosis of acute myocardial infarction was confirmed by E C G which showed large Q waves in leads II, III, aVF, and the V leads, together with RST elevation and T inversion in leads I, aVL, V_5 and V_6 (fig 1d) The patient was treated with bed rest, anticoagulants were not prescribed On July 16 there was a loud pansystolic apical precordial murmur, but no evidence of congestive cardiac failure Perforation of the I V S was diagnosed Next day there was deterioration with a fall in blood-pressure and rise of jugular venous pressure Despite symptomatic treatment, the patient's condition did not improve E C G taken on Aug 7 (fig 1e) showed no evidence of further infarction She died next day

Necropsy

The heart weighed 330 g , the right ventricle was slightly hypertrophied In the upper portion of the left ventricle the muscle was hypertrophied, but the apex involving the anterior, lateral, and posterior walls was thin (0 2 cm), being made up of fibrotic tissue and thickened endocardium The apex of the left ventricle was part of a ventricular aneurysm The septal wall was also thin, being perforated at its lowest portion by a fibrin covered rent 0 8 cm long The coronary arteries were atheromatous with evidence of recanalisation

Postmortem diagnosis rupture of I V S following recent myocardial infarction and old myocardial fibrosis

Case 6 —A retired engineer of 67 was admitted on April 20, 1959 He had had hypertension since 1941 He had been investigated for anæmia in 1954, when his blood pressure was 170/110 mm Hg Manifestations of cerebral arteriosclerosis were observed over the following years He had never had angina pectoris or undue effort dyspnœa On April 18, 1959, he had an attack of severe pain between the shoulder-blades, associated with dyspnœa This became worse, and admission was requested

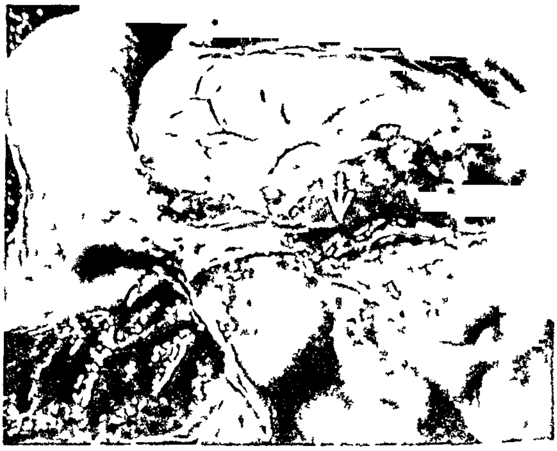

Fig 4—Case 4: fresh thrombus in right coronary artery

Examination and course —The patient was an obese apyrexial man in no obvious distress Pulse-rate 100 per min regular, blood pressure 180/110, jugular venous pressure raised to 4 cm, apex beat 5th left intercostal space in the anterior axillary line, heart sounds normal without murmurs or thrills E C G (fig 1f) showed RST elevation in II, III, aVF, V_1–V_6, with T inversion in I and aVL, confirming the clinical diagnosis of acute myocardial infarction Anticoagulant therapy was instituted During the next four days he became confused On April 25 there was sudden deterioration with arrhythmia and fall of blood-pressure to 110/70 E C G (fig 1g) showed atrial fibrillation, RST elevation in I as well as in all other leads, with increased elevation in leads II, III, aVF, V_1–V_6 Blood urea was 300 mg. per 100 ml. On May 1 there was a loud pansystolic murmur obscuring the normal heart-sounds, being best heard at the left sternal edge in the 4th left interspace. There were some slight signs of congestive cardiac failure. Rupture of the I.V.S. was diagnosed. The patient was digitalised, but slowly deteriorated. He lapsed into coma, and died on May 7.

Necropsy

The heart was enlarged, weighing 750 g. There was extensive infarction of heart muscle involving the apex, lower half of the anterior left ventricular wall and septum, and lower two-thirds of lateral and posterior left ventricular walls. An irregular perforation of the I.V.S. was found in its lowest part, measuring 1.5 cm. across. The coronary arteries were narrowed throughout. There was incomplete obstruction of the left main coronary artery, 2.5 cm. distal to the origin on the descending branch which was completely occluded.

Postmortem diagnosis: cardiac infarction with perforation of the I.V.S., generalised atherosclerosis.

Case 7.—A carpenter of 61 had been without exertional chest pain, or dyspnœa until May 2, 1959, when he felt severe epigastric pain without nausea, sweating, or vomiting. He was seen in a casualty department where his blood-pressure was 200/120 mm. Hg, and there were no other abnormal physical signs. He was treated with sedatives and antacid powders. Vague left precordial discomfort developed over the next two days, and he was admitted on May 4, 1959.

Examination and course.—The patient looked fit and was in no obvious pain. There was no cyanosis and the limbs were warm, his blood-pressure was only 90/60, pulse-rate 120, regular, no jugular venous pressure, lung bases dry. A systolic thrill was felt over the lower sternum, and the heart-sounds were obscured by a loud pansystolic murmur maximal over the apex, radiating to the axilla. Acute myocardial infarction with subsequent rupture of the I.V.S. was diagnosed. E.C.G. (fig. 1h) showed the greatest RST elevation in V_3, but it was also present in leads II, aVF, and all the V leads, together with T inversion in these leads, and a distinct QS pattern in V_1 and V_3. Anticoagulant therapy was started, and later, in view of congestive cardiac failure, digitalis was added. Despite this, the congestive cardiac failure proved intractable and attacks of acute left ventricular failure supervened. Hypotension developed, and, after a hæmatemesis, the patient died on May 31.

Necropsy

The pericardial sac was found to contain a little blood, with petechial hæmorrhages over the posterior surface of the heart. The heart (418 g.) showed early right ventricular hypertrophy. There was a triangular tear in the lower part of the I.V.S. about 1.5 cm. across, the upper edge being a little rounded while the lower edges were rough. There was obvious recent infarction of the surrounding septum and anterior wall of the left ventricle which showed some generalised hypertrophy. All coronary arteries were atheromatous, with obliterations, in one place, of the lumen of the anterior descending branch. In addition, there was evidence of congestive cardiac failure, and of gastro-intestinal hæmorrhage without obvious cause.

Postmortem diagnosis: rupture of the I.V.S. following recent acute infarction of the left ventricle and septum due to coronary occlusion, also acute gastrointestinal hæmorrhage.

The data on these 7 cases are summarised in the accompanying table.

Discussion

Incidence of Septal Infarction and Rupture

Myocardial infarction often encroaches on the septum. Series only partly supported by necropsy confirmation depend on E.C.G. findings which are open to different interpretation. On available necropsy material, the incidence of septal involvement may be as high as 90%, with 30% showing massive septal infarction (Osher and Wolff 1953), but septal rupture rather than mere infarction is uncommon. Edmondson and Hoxie (1942) could collect only 13 cases (1.5%) in a series of 864 necropsies on patients with unhealed myocardial infarcts. Septal rupture is found in about 60% of cases of death due to cardiac rupture (Oblath et al. 1952). Though septal infarction is fairly common, septal rupture is relatively rare. Survival from such a rupture—even for short periods—is not often reported. Reviews of I.V.S. perforation include those of Sanders et al. (1956) and Sahagun and Burns (1956), and small series and isolated case-reports are often published—e.g., Goldman (1959) and Swithinbank (1959). But the total number of reported cases of survival, even for a few hours, after septal rupture is probably still less than 200.

ANALYSIS OF 7 CASES

Sex-distribution	5 men, 2 women
Av. age (yr.)	64
Hypertension before recent infarction	Only 1 definite
After recent infarction	
Persistent hypertension	3
Anticoagulants	1
Pressor agents	0
Av. interval (days) between infarction and perforation	About 5
After perforation	
Mode of onset of symptoms	Insidious in 5, sudden in 2
Systolic murmur	7
Systolic thrill	3
Diastolic murmur	Nil
Congestive cardiac failure	6: 2 also had left ventricular failure
Left ventricular failure	2, both with congestive cardiac failure
Other complications	1 jaundice and hæmorrhage 1 uræmia 1 hæmorrhage
Av. period of survival after perforation	29 days (range, from few hours to 68 days)
Postmortem findings	
Heart weight	Av. 489 g. 6 cases above normal of 330 g.
Old infarction	Only 2 definite
New infarction	7 involving left ventricle and septum
Site of I.V.S. perforation	6 lower septum, 1 upper septum
Size of I.V.S. perforation	0.8–4 cm. diameter
Size of arterial obstruction	Variable

Treatment and Prognosis

The prognosis in myocardial infarction with septal rupture is poor: 50% of patients die in the first week (Sanders et al. 1956) as against 11.5% in an unselected series with myocardial infarction alone (Bland and White 1941). Of the present group of 7 patients, however, only 2 died in the first week. The longest survival was sixty-eight days, and the average survival twenty-nine. Long-term survival is quite exceptional: patients who have lived four years (Zucker et al. 1952), five years (Wood and Livezey 1942), and 1 who was alive after six and a half years (Schlappi and Landale 1954) have been recorded. Progressive congestive cardiac failure is the rule in survivors, and death from this is usually not long delayed, though routine medical treatment may be of temporary value. With advances in surgical and anæsthetic techniques, surgical treatment will be increasingly feasible. There is already a report by Cooley et al. (1957) of a patient who survived six weeks after such an operation, and at necropsy the perforation was found to have been well repaired, with a small recurrent defect.

Symptoms and Signs

Bond et al. (1953) state that septal rupture associated with cardiac infarction can occur at any age, but that the average age of recorded cases is the same as that of uncomplicated cardiac infarction—i.e., 61. This tallies well with the present series where the average age at death was 64. Perforation of the I.V.S. is very uncommon under 50, and it affects twice as many men as women. Of the present series, 5 were men. In most of the reported cases of perforation complicating acute myocardial infarction the patient's condition suddenly became worse, usually in the first ten days after the original infarction. Surprisingly enough, only 2 of the present 7 cases showed any sudden change in symptoms All perforations occurred, however, in the first two weeks after infarction, and 6 out of 7 in the first week

The full clinical picture is easy to recognise A patient with recent myocardial infarction is found to deteriorate, often with symptoms suggesting further infarction, commonly chest pain recurs with associated dyspnœa The patient is shocked and hypotensive, and may show rhythm changes, an apical systolic thrill is commonly found On auscultation, a loud pansystolic murmur is heard over the whole precordium, but especially at the left lower border of the sternum, this murmur is reduced in intensity if the blood-pressure is low The second pulmonary sound may be accentuated Signs of congestive cardiac failure quickly develop, but acute pulmonary œdema due to left ventricular failure is reported to be uncommon Of the patients in this series, 6 had congestive cardiac failure, and in 2 of these left ventricular failure developed later

Electrocardiographic Changes

The diagnosis of I V S rupture may be impossible to confirm by routine methods during life Nevertheless, E C G changes may be of great help, at least in giving evidence of septal infarction Osher and Wolff (1953) reviewed the E C G and pathological findings in 35 cases of myocardial infarction

The hearts were examined by the Schlesinger method of injection-plus-dissection, supplemented by multiple microscopic sections of the myocardium They found that conduction defects were diagnostic of septal infarction (1) when bundle-branch block or high-grade atrioventricular block appeared following myocardial infarction (2) when complete right bundle-branch block was associated with conspicuous Q waves in the right precordial leads or left bundle-branch block was found with left precordial Q waves and (3) when left bundle-branch block occurred with low voltage in limb and left precordial leads QS deflections with abnormally elevated RST segments in right precordial leads without bundle-branch block suggested septal infarction A further characteristic of septal infarction was simultaneous anteroseptal and posterior infarction, though this was rare Evidence of anterior together with posterior infarction indirectly suggested septal involvement

Abrahams (1957) claimed that T inversion in CR_4 with variable T inversion of CR_1 and CR_2 in the absence of Q or RST changes is evidence of restricted septal infarction As other criteria have been suggested—e g , Myers et al. (1949)—it is clearly impossible as yet to define the exact E C G changes of septal infarction

The E C G tracings of the 7 patients in this series are reproduced in fig 1 There is no evidence that septal perforation alters the E C G pattern of septal infarction

Confirmation by Catheter Studies

Only by cardiac catheterisation can the diagnosis of septal rupture be proved rather than presumed In the case of Muller et al (1950), such proof was obtained The patient survived fifteen months, and necropsy confirmed the presence of septal rupture Sanders et al (1956), however, cited a case where catheterisation was unhelpful

Differential Diagnosis

As Sahagun and Burns (1956) suggest, differential diagnosis is limited Only a handful of conditions associated with acute myocardial infarction might give rise to confusion, of these pericardial friction rub and functional mitral incompetence should not present undue diagnostic difficulties

Rupture of a papillary muscle may however, simulate I V S rupture Askey (1950) found that, in 27 out of 29 reported cases, papillary rupture complicated cardiac infarction The murmur may be either systolic, diastolic, or both, though the murmur of ruptured I V S is almost invariably purely systolic Should there be a diastolic murmur in the presence of septal perforation, it is usually due to coincidental pre-existing left ventricular aneurysm (Zucker et al 1952, Scherf and Brooks 1949) Moreover, in cases with ruptured papillary muscle, there is sudden collapse with acute left ventricular failure, and the systolic murmur is never loud enough to give rise to a palpable thrill This is in contrast to acute septal perforation where a thrill is common, where the development of complications may be insidious, and where congestive cardiac failure is much commoner than left ventricular failure An intraventricular thrombus, appearing after acute cardiac infarction, may mimic the physical signs of ruptured I V S (Loeper et al 1940), but this complication is probably even rarer than rupture of a papillary muscle Other conditions, such as pre-existing ventricular septal defect, ventricular septal defect after bacterial endocarditis, rupture of a sinus of Valsalva, rupture of aortic cusps, and rupture of chordæ tendineæ, are not associated with acute myocardial infarction, though certain of their features may resemble those of septal perforation following myocardial infarction

Predisposing Factors

Septal infarction is not uncommon, occurring in 70–90% of cases of acute myocardial infarction, and septal rupture might be expected to take place more often than it does Mallory and White (1939) showed that, during the first week after infarction, there is muscle necrosis and round-cell infiltration, removal of necrotic tissue and replacement by connective tissue predominate over the next five weeks Rupture of the heart is commonest in the first week Presumably, speed and effectiveness of repair depend on the blood-supply that is reaching the infarcted area The I V S is supplied anteriorly by perforating branches from the anterior descending coronary artery, and posteriorly by perforating branches from the right This double blood-supply is probably one of the reasons why septal rupture is relatively rare anastomotic channels may grow out quickly into the infarcted area from the unaffected coronary artery and promote healing, rather than necrotic breakdown

Edmondson and Hoxie (1942) reviewed the effect of hypertension on cardiac rupture in acute myocardial infarction, and found that persistence of hypertension after infarction made for a poor prognosis, while hypertrophy or previous scarring of the heart appeared to offer some protection against rupture In the present series, 3 patients had diastolic pressures of 110 mm Hg or over after infarction and before perforation, 2 patients showed definite evidence of old infarction Infarction need not be of full thickness to lead to rupture (Wessler et al 1952, Oblath et al 1952), shearing stresses may tear a partially infarcted muscle Such stresses are apparently greater in the ventricular walls than in the septum, which may be another reason why rupture outwards is commoner than across the septum Pressure gradients across myocardial muscle are also important since the septum is partially splinted by the right ventricular pressure against the high left ventricular pressure, the gradient across the septum is less than across the ventricular walls The series of Wessler et al (1952) underlines these points of 19 ruptures associated with acute myocardial infarction, all were of the left ventricle, but only 5 were septal, the remaining 14 rupturing into the pericardial sac

Pressor Agents and Anticoagulant Therapy

Do routine methods of treatment influence the chances of cardiac, and especially septal, rupture? Since pressure in the left ventricle may exert a great influence it follows that hypotension should protect from rupture Similarly, overenthusiastic use of pressor agents in the first few days after acute myocardial infarction might materially increase the risk of rupture, as this is the period before adequate repair has taken place Lange and Aarseth (1958) published a somewhat disturbing report on a carefully controlled series of 141 patients with acute cardiac infarction, half of whom received anticoagulants the incidence of spontaneous rupture in those patients was twice that in the controls Honey and Truelove (1957) showed, however, that patients with myocardial infarctions who do not receive anticoagulant treatment run a greater risk of dying from thromboembolic phenomena, such as pulmonary infarctions Only 1 patient in the present series was given anticoagulants after the infarction and before perforation of the I V S

Conclusion

Survival after septal perforation following cardiac infarction may not be so uncommon With advances in techniques, surgery of this condition may become feasible Accurate diagnosis will, therefore, assume greater practical importance

Summary

7 cases are described in which rupture of the interventricular septum followed acute myocardial infarction

6 of these cases were diagnosed during life

A plea is made for early accurate recognition of this not so uncommon condition

My thanks are due to Dr J R Bolton, Dr Donald Hunter, Dr J M Ledingham, and Dr A L Wyman for allowing me to discuss their patients, and to the various pathologists who conducted the postmortem examinations I am particularly grateful to Dr A L Wyman for his encouragement with this paper Of the 7 patients here described, I saw only cases 3, 4, 5, and 7, all of whom were under Dr Wyman's care I also thank the electrocardiographers and photographic technicians of the various hospitals where the patients were treated, I should especially like to acknowledge the help of Mr Raymond Ruddick, of The London Hospital photographic department

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TYPE-3 ADENOVIRUS INFECTION

T M Bell
B Sc Glasg
LECTURER IN BACTERIOLOGY

Grace Turner
M B Aberd
TRAINEE ASSISTANT

A Macdonald
M.A, M D Aberd
PROFESSOR OF BACTERIOLOGY IN THE UNIVERSITY OF ABERDEEN

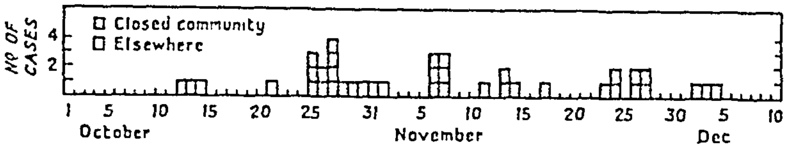
D A Hamilton
M B Aberd
GENERAL PRACTITIONER, AUCHINBLAE

Clinical differentiation of virus infections of the upper respiratory tract is notoriously difficult, and only occasionally, as in the diagnosis of influenza, are laboratory investigations considered likely to be rewarding This is an understandable view in infections which are often mild, of short duration, and unaffected by treatment The recognition of an increasing number of new respiratory agents may lead to a better understanding of these infections, but, temporarily at least, the doctor's difficulties remain since ætiological relations have still to be firmly established, and we know little about their incidence Certain members of the adenovirus group of agents should escape these general criticisms, for a few of them are known to cause recognisable illnesses which have been studied in several countries

Infection with the type-3 adenovirus in children of school age is often described as pharyngoconjunctival fever—a useful name but one which does not suggest the wider range of symptoms which may occur, as in the present outbreak In this as in other areas adenovirus infections caused by types 1 and 2 are often unrecognised infections of young children, or single sporadic cases, whereas localised outbreaks of clinical disease are usually caused by other serological types, such as types 3 and 8 There were many cases of type-3 infection in English schools in 1955 (Kendall et al 1957), and in this area the last known outbreak, caused by type 8 (Bennett et al 1957), was in 1956 Such a long interval between outbreaks of clinical infection does not help familiarity, and there is also need for more rapid means of laboratory confirmation if the adenovirus infections are to be recognised more often and removed from the mass of undifferentiated febrile catarrhs or influenza-like illnesses

Clinical Details

From Oct 13 to Dec 4, 1959, thirty-nine cases of acute febrile illness were seen in a rural practice, and of these thirty-two were in a community of ninety-five boys aged 8–13 years The ill boys complained of headache, dizziness, photophobia, and, in many cases, stuffed nose or sore throat Temperatures ranged from 99° to 104°F, with usually an M-shaped curve, and most of the boys were flushed during the first rise Most also had back, limb, and neck stiffness, but only one child had positive Kernig and Brudzinski signs The expected cervical adenitis was not a prominent feature Many of the boys had obvious pharyngitis, while several complained of earache and a few developed bullæ on the eardrums Definite conjunctivitis was noted in only two cases Six either vomited or had gastrointestinal symptoms, and most complained of nausea The illness usually lasted about 5 days, and all made a complete recovery without treatment other than rest in bed The figure shows the onset of illness of cases within the community, and in those seen outside The incubation period was thought to be about 7–8 days, but it was not possible to determine the means of spread of the infection either within the community or among children outside There was no possibility of spread from a swimming-pool It seemed likely that the infection



Type-3 adenovirus infection in a rural practice

required close personal contact by an agent which was not highly infectious Seven sporadic cases were seen outwith the community

Laboratory Investigations

Since the cases were some distance from the laboratory, throat and eye swabs and sample of fæces were sent by post These were examined for bacterial pathogens as well as for viruses Acute and convalescent samples of blood were collected, usually with an interval of 25 days

For attempted virus isolation two types of tissue-culture cells—(1) HeLa cells, or (2) human embryonic kidney and liver cells, or human amnion—were used routinely A standard series of media was used for culturing all four types of cells They contained lactalbumin hydrolysate 0 5%, calf serum 2%, 10%, or 20%, and Hanks' BSS together with the usual antibiotics Cell suspensions were prepared using trypsin 0 25%, and after growth two tubes of each cell line were inoculated with the supernatant fluid from a 20% suspension of fæces or fluid from extracted eye or throat swabs After incubation at 37°C the tubes were examined daily and compared with controls

Isolated viruses which had the general characteristics of the adenovirus group were typed by neutralisation with type-specific antisera prepared in our laboratory with prototype strains obtained from Dr H G Pereira Sera against types 1–11 and 14 were used, two tubes per type with the usual controls Acute and convalescent samples of serum from patients were tested both for complement-fixing and neutralising antibodies Two antigens prepared against the prototype-3 virus and a type-3 strain isolated during the outbreak were used for complement-fixation tests which were done in plastic plates by standard methods (World Health Organisation 1959) Neutralisation tests with all sera were also performed by standard methods against a strain isolated during the outbreak and also against prototype strains 1, 3, 4, 7, 10, and 14 The suspensions of virus for serological tests were grown in human embryonic liver cells

Results

Because specimens from the cases were obtained at various stages during the outbreak the laboratory findings were thought to sample the infection throughout its course From twelve boys, 11 samples of fæces, 5 throat swabs, and 1 conjunctival swab were examined Blood samples were taken from five cases at 25 days' interval, and from two others at 2 months, from one patient only a convalescent sample was received

At the beginning of the outbreak Coxsackie-B5 virus was isolated from one boy, and a fourfold rise of neutralising antibody was demonstrated in his serum The possibility that other boys in the outbreak could be similarly infected was excluded both by failure to isolate any other Coxsackie virus, and by negative serological tests, in the eight cases examined

All other viruses isolated during the outbreak proved to be type-3 adenovirus The 1 conjunctival swab was positive, and 1 out of 5 throat swabs, and 10 out of 11 fæcal specimens were also positive Type-3 adenovirus was thus isolated from about a third of the cases during the outbreak, and, apart from the single instance of Coxsackie B5, no other virus or bacterial pathogen

HeLa cells are usually recommended for the isolation of adenoviruses, but in several laboratories difficulty has been experienced in maintaining these cells in continuous culture over a long period, and, which may be more important, in maintaining them in a state of full sensitivity, suitable for recovery of adenovirus We were thus interested to know not only if our own routine strain of HeLa cells was an effective tissue for this purpose but also to compare it with other tissue-culture cells at our disposal As we were not able to use all four types of tissue culture for each of the original isolations a 20% suspension of fæces from cases was stored at −20 C for further tests One specimen arrived in the laboratory 10 days after collection when virus had already been isolated from the same patient, and thus specimen was subsequently left at 4 C for 2 months before the suspension was prepared (no 7 in table I) It was thus possible to examine all four tissue cells simultaneously using aliquots of the inoculum for each pair of tubes of the different tissues Only fæcal specimens could be tested in this way, for there was not enough material from throat or conjunctival swabs The results, in italics, in table I show the time taken in days for the original isolation in the particular tissue found to be first positive The other figures show the direct comparison of the four tissues under identical conditions All tubes were examined daily and the time was reckoned from the day on which at least one of a pair of tubes showed complete and typical degeneration

From table I it is clear that both human embryonic kidney and liver cells provided more rapid evidence of adenovirus infection and that the strain of HeLa cells employed was not appreciably better than human amnion cells for this purpose Many factors may influence the rapidity of isolation of adenovirus, including the size of inoculum (which in this case was not known), the type and strain of tissue cells, and the composition of the media used to grow and maintain the cells From experience of several lines of HeLa cells the one in use at this time was thought to be of about average sensitivity, but Grayston et al (1958) have emphasised the variability of such cells There was no difference between the four tissues in the number of viruses isolated—the differences being confined to the time taken for isolation

The demonstration of a rising titre of antibody for the type of virus isolated during the course of illness does not prove the virus and illness are causally related but it is valuable evidence The serological tests shown in table II were done with a strain of type-3 virus isolated during the outbreak, and also with the prototype-3 strain Neutralisation tests were also performed on all samples of serum against prototypes 1, 4, 7, 10, and 14

TABLE I—TIME REQUIRED (DAYS) FOR DEMONSTRATION OF TYPE-3 ADENOVIRUS IN FÆCES

No of specimen	Tissue culture			
	HeLa	Human amnion	Human embryonic kidney	Human embryonic liver
1	8	8	5	3 *(3)*
2	8	4	5	2 *(7)*
3	9	9	5 *(5)*	3
4	–	7	3 *(5)*	2
5	5	7	3 *(3)*	2
6	9 *(7)*	9	6	3
7	16	17	7	–
8	7	6 *(7)*	4	3
9	11	13 *([illegible])*	–	4
10	6	5	3 *(4)*	2
Mean isolation time	9 6	9 7	5 3	3 6

TABLE II—COMPLEMENT FIXING AND NEUTRALISING ANTIBODIES IN CASES EXCRETING TYPE-3 ADENOVIRUS

Case	Complement fixation with		Neutralisation of	
	Prototype 3	Outbreak 3	Prototype 3	Outbreak 3
1	N D	<1/32	<5/40	5/40
2	<4/128	<1/128	<5/20	5/40
3	<4/128	<1/128	<5/20	<5/[illegible]0
4	8/64	8/64	<5/80	<5/80
5	<1/16	<1/32	<5/20	5/40
6	<1/32	4/64	<5/80	<5/80
7	<4/8	<4/16	<5/40	<5/40

1/32 = Acute/convalescent serum antibodies, N D = not done viruses Minor heterotypic rises of antibody were obtained with all of these types, except type 1, and there was no evidence that any of them was concerned in the outbreak.

These results show that infection with type-3 virus occurred when the boys had their symptoms, and together with the results of virus isolation they strengthen the view that this was the cause of illness Proof of the ætiological significance of isolated viruses in a particular adenovirus disease also requires statistical correlation, and in this outbreak only a third of the boys was investigated Nevertheless epidemiological features of the infection, and the failure to isolate any bacterial pathogen or any other virus apart from the single strain of Coxsackie B5, are all consistent with the other evidence showing that the outbreak was caused by type-3 adenovirus

Discussion

The name pharyngoconjunctival fever was given by Bell et al (1955), and has been familiar for outbreaks of type-3 adenovirus infection, particularly in schoolchildren Types 7 and 14 adenoviruses have also been found to cause a similar illness The main clinical features of this disease are fever, pharyngitis, rhinitis, conjunctivitis, and enlarged cervical lymph-nodes Of the cases described by Kendall et al (1957) more than 70% complained of sore throat and headache, 97% had enlarged cervical lymph-nodes, and all serologically proved, as distinct from clinical cases, had conjunctivitis In the present outbreak of type-3 infection conjunctivitis was noted in only four of the thirty-two cases, and the virus was isolated from the only eye swab sent for examination Ginsberg et al (1955) have also described an outbreak in which there were no obvious signs of conjunctivitis

Another difference from the usual clinical picture was the common complaint of stiffness in the back, legs, and neck, and this was also found by Forssell et al (1956) and by Barr et al (1958) in Sweden Lumbar puncture was performed in eight of the latter series of cases, but with negative findings It was realised that painful cervical lymph-nodes might cause neck stiffness, but this could not account for the stiffness in back or legs Several workers have noticed that gastrointestinal symptoms may occur, and six of the present thirty-two cases either vomited or had abdominal symptoms, while most complained of nausea Clearly it might be misleading if pharyngoconjunctival fever was to be considered the only manifestation of outbreaks of type-3 adenovirus infection, and until more is known it would be wise to think of the triad of symptoms as indicating one of a possible range of clinical syndromes in schoolchildren

The isolation of adenovirus is often considered fairly simple, and primary explant cultures of human amnion, human respiratory tissues, or serially progagated cell cultures such as HeLa cells have been recommended (World Health Organisation 1959) HeLa cells have been most widely used, but Grayson et al (1958) have found that some 20% of adenoviruses from clinical material required 15–33 days for isolation They also demonstrated that different laboratory lines of HeLa cells varied in their sensitivity to adenovirus, using one line only 9 type-4 adenoviruses were recovered, while with a second line 17 adenoviruses were isolated from the same clinical specimens Contamination of stock HeLa cells with pleuropneumonia-like organisms is common, and this must also be considered Several different lines of HeLa cells have been used in this laboratory, and the strain employed in the present investigation was thought to be of average sensitivity It is known that the composition of the culture media for these cells affects the quantity of virus produced, and we have used calf-serum which is believed to contain inhibitors against adenoviruses We were, however, unable to show that such inhibitors appreciably affected the rapidity of isolation of type-3 adenoviruses Using the same growth and maintenance medium for HeLa, human amnion, and human embryonic kidney, and the same maintenance medium for liver cells we found a consistently more rapid rate of isolation from all the types of clinical material tested with the two human embryonic tissues

It is usually recommended that for adenovirus recovery it may be necessary to incubate tissue cultures for up to a month, or alternatively to make several blind passages of culture fluids at short intervals In the present investigation it was necessary to do this only when attempting to isolate virus from some of the throat swabs While such procedures are necessary when the amount of virus in clinical material is very small, it is also desirable to try to ensure that the virus is propagated on as sensitive tissue cells and possible

Summary

In a community of ninety-five boys thirty-two developed symptoms suggestive of pharyngoconjunctival fever, except that conjunctivitis was rare and muscular stiffness was common Type-3 adenovirus was isolated from eleven boys, and seven of them showed confirmatory rises in complement-fixing and neutralising antibodies

Type-3 adenovirus was isolated more quickly by using human embryonic tissue-cultures than with a strain of HeLa cells

We wish to thank Miss Helen Martin for technical help

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A LEUCINE-SENSITIVE INSULIN-SECRETING TUMOUR

DAVID MARRACK
M.D Lond
SENIOR LECTURER IN CHEMICAL PATHOLOGY,
THE NATIONAL HOSPITAL, QUEEN SQUARE, LONDON, W C 1

VINCENT MARKS
B M Oxon, M R C.P.E
M.R.C CLINICAL RESEARCH FELLOW IN CHEMICAL PATHOLOGY,
KING S COLLEGE HOSPITAL, LONDON, S.E.5

F CLIFFORD ROSE
M B Lond, M.R.C.P
FIRST ASSISTANT IN THE DEPARTMENT OF NEUROLOGY,
ST GEORGE S HOSPITAL, LONDON, S W 1

Cochrane et al (1956) reported the induction of hypoglycæmia as an abnormal response to *l*-leucine given by mouth to three children and an adult An increase in insulin-like activity of plasma after *l*-leucine administration has been demonstrated in *l*-leucine-sensitive children but not in normal children (Di George et al 1960, Grumbach and Kaplan 1960, Mabry et al. 1960) Butterfield et al (1960) present evidence that *l*-leucine-induced hypoglycæmia in an adult "is due to a *transient* rise in plasma-insulin activity" (our italics) The response to *l*-leucine given by mouth in one of three adults with insulin-secreting pancreatic tumours whom we studied, lends support to this suggestion

Our three patients had been repeatedly observed to have low blood-glucose levels associated with episodes of disturbed consciousness, disorientation, incoordinated movements, and occasionally coma, and these symptoms were rapidly relieved by glucose intravenously All three cases gave a positive response to the glucagon test—i e, *initial hyperglycæmia followed by profound hypoglycæmia* after intramuscular injection (Marks 1960)—and to the tolbutamide test in which a precipitate and prolonged lowering of blood-glucose follows intravenous injection (Marrack 1961)

Only one case showed a precipitate fall of blood-glucose when fed with *l*-leucine (0 1 g per kg body-weight) This patient went into hypoglycæmic coma with convulsions, which had to be relieved by glucose intravenously 30 minutes after the ingestion of *l*-leucine Blood taken from a limb vein whilst the surgeon was manipulating the tumour, and the tumour itself, both had a very high plasma-insulin content (by radio-chromato-electrophoretic immuno-assay) After removal of the tumour this patient had no further clinical attacks of hypoglycæmia, and blood-glucose levels were within the normal range When the oral leucine test was repeated after operation the blood-glucose level did not drop, and there was no detectable clinical change

Discussion

The presence of an insulin-secreting tumour cannot be excluded because hypoglycæmia is precipitated when *l*-leucine is given by mouth Schwartz et al (1958) reported the precipitation of hypoglycæmia by *l*-leucine in two adults who were later found to have pancreatic islet-cell tumours One of these had an islet-cell carcinoma with metastases, and the leucine sensitivity persisted after operation A case of islet-cell adenoma similarly examined by Monro (1960) was not leucine-sensitive

The probability is that in our patient before operation oral *l*-leucine initiated the release of extra insulin from the tumour But if this is so there must be at least two biochemical mechanisms by which insulin can be released, since in only one of our three cases was the tumour stimulated by leucine

The rat's blood-glucose level normally falls after *l*-leucine administration (Cochrane 1960) In essential leucine sensitivity of children there seems to be a genetically determined abnormality which gives them an additional mechanism for activating the release of insulin Presumably a similar biochemical mechanism may be acquired by the abnormal cells of some insulin-secreting tumours

After rapid intravenous injection of insulin or tolbutamide, hypoglycæmia does not appear in less than 25 minutes The time-interval between oral administration of leucine and the appearance of hypoglycæmia in sensitive individuals suggests that only part of the insoluble *l*-leucine can have been absorbed before the insulin-releasing mechanism is activated Such a view is consistent with the observations of Woolf (1960) and of Cochrane (1960)

Di George et al (1960) said "It is not known whether this net increase in insulin produced by leucine represents accelerated synthesis or decreased breakdown" The evidence from our patient suggests that the increase in plasma-insulin arises from accelerated insulin release rather than from accelerated insulin synthesis, and this is incompatible with the concept of decreased insulin breakdown in sensitive subjects

Conclusions

In a patient of any age the finding that *l*-leucine induces hypoglycæmia does not exclude the presence of an insulin-secreting tumour A positive response to the glucagon and tolbutamide tests is strongly in favour of an insulin-secreting tumour, whereas evidence of familial hypoglycæmia favours essential leucine sensitivity

Hypoglycæmia induced by *l*-leucine in sensitive individuals seems to be due to accelerated insulin release rather than to increased synthesis or decreased breakdown

We are grateful to Dr Ellis Samols, of the department of medicine, Royal Free Hospital, London, W C 1, for the plasma insulin assays

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Preliminary Communication

AN 11 β-HYDROXYLASE INHIBITOR IN THE TREATMENT OF RESISTANT ASCITES

2-METHYL-1, 2-bis(3-pyridyl)-1-propanone-ditartrate (Su-4885), a synthetic analogue of amphenone B, selectively inhibits 11 β-hydroxylation of adrenal steroid precursors[1,2] and therefore presumably inhibits aldosterone production Amphenone has been used as an aldosterone antagonist but was finally abandoned because of its untoward side-effects[3] Su-4885 and its hydrochloride, Su-8874 ('Metopirone'), are considerably less toxic and might therefore be considered as diuretics We have assessed metopirone as a diuretic, alone and in combination with chlorothiazide and spironolactone, in two patients with cirrhosis and resistant ascites

THE STUDY

The patients were a 52-year-old man and a 36-year-old woman with cirrhosis of unknown ætiology Ascites had been present for at least 12 months before treatment, and paracenteses had been necessary

They each excreted in the urine less sodium than 1 mEq per 24 hours during a control period of 3 days on a constant 22 mEq dietary intake (see figs 1 and 2), and this did not increase when chlorothiazide 2 g daily was given The first patient was also resistant to the combination of chlorothiazide 2 g daily, spironolactone 400 mg daily, and mannitol 2 litres of 10 solution intravenously After a further control period of 3 days, both patients started prednisone 5 mg twice daily

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Their urinary sodium and clinical status did not change, and after 3 days metopirone (900 mg t d s) was added After 4 days the first patient showed no increase in urinary sodium, and the second showed a very slight increase to 5 mEq per 24 hours In both patients the clinical state was unchanged

When chlorothiazide was added in a dosage of 2 g daily, both patients began to lose weight and their urinary sodium excretion increased The first patient's sodium diuresis was slow, reaching 40 mEq daily, but after the addition of two mannitol infusions the sodium excretion increased to 110 mEq per day He then lost weight steadily, passing 60–70 mEq of sodium daily for 3 weeks This continued during 32 days of metopirone therapy, there being no sign of resistance to the drug In the second patient metopirone caused a sodium excretion of 75–100 mEq daily for 2 weeks

At this stage spironolactone (600 mg per day in the first patient and 400 mg per day in the second) was added to the combination A dramatic increase in sodium excretion was seen, reaching a peak of 175 mEq per day in the first patient and 290 mEq per day in the second, and body-weight decreased dramatically The first patient required potassium supplements after 2 weeks' chlorothiazide and metopirone therapy, as the serum-potassium level had fallen to 2 4 mEq per litre The second patient was given potassium supplements throughout

After 3 days' combined treatment metopirone was stopped and the patients continued on spironolactone, chlorothiazide, and prednisone The 24-hour urinary sodium excretion fell in both patients to the levels obtained with metopirone without spironolactone, and the urinary sodium excretion was not further reduced when the prednisone was stopped

Neither patient showed any side-effects from continuous metopirone therapy, and clinical evidence of adrenal insufficiency was not seen when prednisone therapy was stopped Both patients showed considerable clinical improvement with clearance of their ascites, the weight-loss averaging 20 kg , and both patients' serum-albumin levels rose from less than 2 6 g to more than 3 5 g per 100 ml

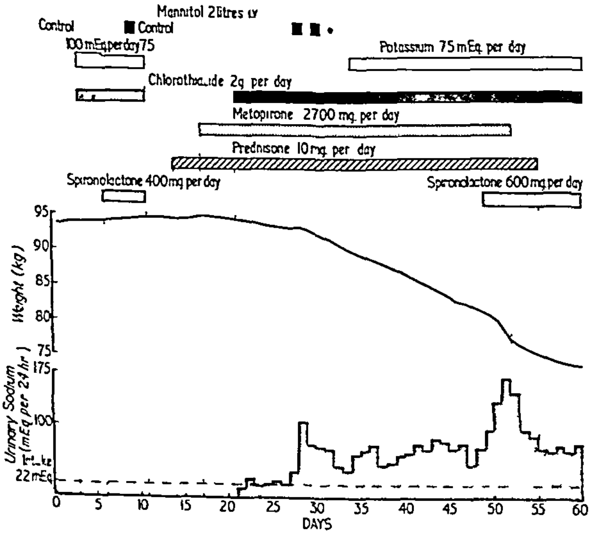

Fig 1—A 52-year-old man with cryptogenic cirrhosis and intractable ascites requiring repeated paracenteses over 12 months

The patient was completely resistant to chlorothiazide alone or in combination with spironolactone 400 mg per day, and mannitol 2 litres 10% intravenously He showed no response to prednisone and metopirone, but with the addition of chlorothiazide he finally began to lose weight and to excrete sodium Mannitol considerably potentiated this diuresis, but after 2 weeks he required potassium supplements to control hypokalæmia The addition of spironolactone 600 mg per day produced a dramatic loss of weight and of urinary sodium which quickly reverted to previous levels on the withdrawal of metopirone from the combination The patient was not resistant to the increased dose of spironolactone when combined with chlorothiazide

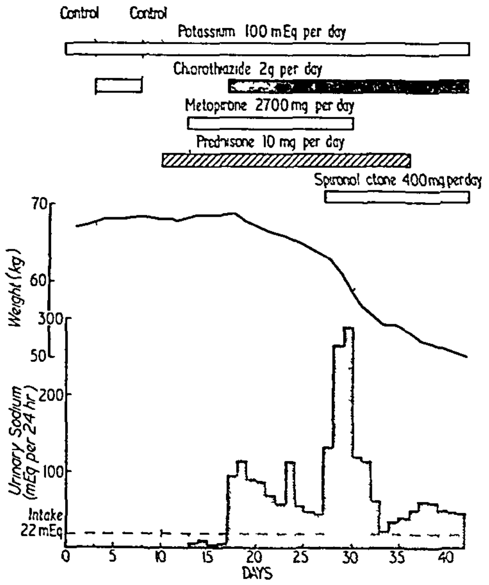

Fig 2—A 36-year-old woman with cryptogenic cirrhosis and resistant ascites

The patient was completely resistant to chlorothiazide alone, and showed only a small sodium diuresis when given prednisone and metopirone The addition of chlorothiazide caused a steady weight-losing sodium diuresis which was even further potentiated by the addition of spironolactone 400 mg per day The withdrawal of metopirone resulted in a fall in urinary sodium excretion to previous levels The patient responded less dramatically to spironolactone and chlorothiazide than to metopirone and chlorothiazide Prednisone withdrawal did not affect the sodium diuresis

DISCUSSION

Metopirone alone caused a slight urinary sodium increase in one patient, and no change in the other It was therefore clear that, like the other aldosterone antagonist spironolactone,[4] an additional diuretic, such as chlorothiazide, acting on the proximal tubule was necessary to promote diuresis

Metopirone inhibits 11 β-hydroxylation in adrenal steroid biosynthesis and so prevents the formation of 11-oxycorticoids (cortisol, corticosterone, and aldosterone) The precursor of cortisol, 11-desoxy-17-hydrocorticosterone (compound S), and the precursor of corticosterone, 11-desoxycorticosterone (DOCA) therefore accumulate The fall in circulating cortisol and corticosterone releases the anterior pituitary gland from its normal feedback control mechanism and increased corticotrophin secretion follows This results in further increased adrenal synthesis of the 11-desoxycorticosteroid precursors which are ineffective in suppressing corticotrophin production [5,6] This explains the necessity of giving prednisone with metopirone as a substitute for cortisol so that corticotrophin secretion is not increased and the 11-desoxy precursors do not accumulate

Aldosterone secretion is probably not under the control of corticotrophin,[7] and it would therefore not be affected by prednisone administration Patients retaining fluid

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4 Shaldon S McLaren J R., Sherlock, S *Lancet* 1960, i 609
5 Bissel G W Scott, A L Farnsworth, W E Winkler I N Y *St J Med* 1959 59 3596
6 Liddle G W Herschel L E, Kendall J W, Williams, W C. Townes A W *J clin Endocrin* 1959, 19, 875
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have a stimulus to aldosterone secretion, and if this continued when metopirone was given, one would theoretically expect that the 11-desoxycorticoid precursors of aldosterone would accumulate (this is a theoretical consideration as the 11-desoxycorticoid precursor of aldosterone has not yet been isolated) The continued effectiveness of metopirone therapy suggests either that these substances are not potent salt-retaining steroids or, alternatively, that the stimulus to aldosterone secretion has diminished, although this is unlikely as the plasma-volume in these patients decreased

The dramatic potentiation of sodium diuresis when spironolactone was combined with metopirone was most unexpected Spironolactone does not affect adrenal synthesis nor the release of aldosterone, and it is presumed to act by inhibiting the action of aldosterone on the distal renal tubule [8, 9] Thus it is difficult to explain its action in the presence of effective inhibition of the synthesis of aldosterone by metopirone Three explanations are possible

1 When metopirone therapy is prolonged, aldosterone secretion is not effectively inhibited This seems unlikely as the drug did not produce diuretic resistance

2 Spironolactone is not an aldosterone antagonist but it blocks an alternative pathway of sodium reabsorption in the distal tubule This again seems unlikely because spironolactone is known to antagonise infused aldosterone in adrenalectomised animals [10, 11] and in patients with Addison's disease [12]

3 The secretion of the 11-desoxy aldosterone precursor was increased in these patients as they underwent diuresis This substance might not be sufficiently sodium-retaining to allow resistance to metopirone to show but yet be sufficiently active to be blocked by spironolactone, a peripheral aldosterone antagonist Increased diuresis would therefore ensue

The last explanation is the most attractive, and analysis of urine from these patients may allow isolation of the 11-desoxy precursor of aldosterone Further work is in progress to test these hypotheses

SUMMARY

Metopirone is an 11 β-hydroxylase inhibitor which presumably prevents the production of aldosterone by the adrenal gland When used with chlorothiazide, it increased urinary sodium excretion in two patients with cirrhosis and ascites Addition of spironolactone, an antagonist of aldosterone at the renal tubular level, potentiated this diuresis

We should like to thank Messrs G D Searle for financial assistance, and the Medical Research Council for a maintenance grant to J R McLaren We should also like to thank Dr A K Pittman, of Ciba Laboratories, Ltd , for supplies of ' Metopirone '

STANLEY SHALDON
M A , M B Cantab , M R C P
JANET R MCLAREN
B SC Melb

Department of Medicine,
Royal Free Hospital,
London W C 1

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Reviews of Books

A Clinical Prospect of the Cancer Problem Neoplastic Diseases at Various Sites

Introductory Volume Editor D W SMITHERS, M D , F R C P , F F R , professor of radiotherapy in the University of London London E & S Livingstone 1960 Pp 232 37*s* 6*d*

THE quotation at the start of this book neatly introduces its purpose " To explode a myth is accordingly not to deny the facts but to re-allocate them " The myth is that something called " cancer " exists, and the facts that are reallocated are those concerning tissue development, senescence, injury, isolation from control, and clinical observation The word " cancer " is usually applied to an assortment of phenomena, so ill-defined that to group them into one narrow category serves no useful purpose Indeed, to do so is misleading, for it gives rise to the idea that the phenomenon has some unique characteristic not possessed by " non-cancer " The whole concept of the ' malignant cell " is wrong Neoplasms, " benign " or ' malignant ", are better defined as belonging to a category of phenomena within the larger group of tissue maldevelopments and malformations, and arbitrarily defined by certain characteristics of behaviour, not of assumed cellular uniqueness Malformations due to arrest of development come at one end of the scale which passes through those due to differential susceptibility to injury or ageing to hyperplasia and neoplasia " The degree of variation from normal behaviour patterns changes continuously along a scale, with a tendency to independent progression of each characteristic towards complete escape from control The word cancer vaguely covers the most disorganised of these tissue malformations, being applied according to individual preference on the basis of a selection of these degrees of change in several characteristics which are expected to give rise to the greatest danger to the life of the organism Since the meaning of this word can have no precise boundaries this side death, it would be better if we were to abandon its use in communications having some pretence to scientific reporting "

The closely reasoned argument ranges widely over the many special branches of study associated with the investigation of neoplasia The viewpoint is, however, that of the clinician, and there could be no better place to get the right perspective, for the investigation of neoplasm is the investigation of individuals For too long the main emphasis of research has been on the mythical " cancer cell ", trying to find out why it is " cancerous " and how to kill it Chemotherapy research requires, in Professor Smithers' view, much firmer clinical direction into channels where it has a chance of being effective by the correction of particular abnormalities of function or by restoring the lost organisation of tissues

If this view of the problems of neoplasia is accepted (and it seems far more rational than its competitors), it is more profitable to think in terms of neoplasms of various tissues than of *neoplasia in general Carcinoma of the lung* and carcinoma of the bladder have some common characteristics and justify being placed in a single group of " carcinomas ' , but they differ widely in most other characteristics, because the one is a malformation of the lung and the other of the bladder This admirable book is the introduction of a series of volumes on neoplastic diseases at various sites, two of which, on the lung and bladder, have already been published It is a stimulating work

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Diseases of the Nervous System in Infancy, Childhood and Adolescence (4th ed Oxford Blackwell Scientific Publications Springfield, Ill Charles C Thomas 1960 Pp 1548 £11 16*s*)—Dr Frank R Ford's book needs little introduction, and this edition retains the indispensable qualities of its predecessors New concepts of neurology in infancy may cause the whole subject to be rewritten, but until that day Ford stands alone for authority, comprehensiveness and style Although revision has been extensive, some recent work of importance has not found a place—notably in the areas of genetics, and the treatment of congenital malformations and acute infections of the central nervous system

THE LANCET

LONDON 17 DECEMBER 1960

Cardiac Arrest and Resuscitation

DANGEROUS cardiac inaction is due to one of three distinct conditions—complete heart-block, ventricular fibrillation, or asystolic arrest[1,2] Two of these three conditions are now readily treatable Heart-block can be overcome by administering isoprenaline,[3] or better by stimulating the ventricular muscle[4,5] Ventricular fibrillation[2] can be stopped by passing through the heart a depolarising current of sufficient magnitude, voltages of 150-250 being usual Even asystolic arrest will, in some cases, yield to so-called cardiac massage—an inaccurate term, better replaced by " cardiac pumping "[6] or " intermittent cardiac compression "

CALLAGHAN and BIGELOW[7] sparked off the present interest in the treatment of heart-block by artificial pacemaking, and later HOPPS and BIGELOW[1] applied their researches to the needs of cardiac surgery—particularly to the treatment of accidental damage to the bundle of His, which is such a hazard in the repair of ventricular septal defects Direct electrical stimulation of the ventricles to produce pulse-rates exceeding idioventricular rhythm is now accepted by all cardiosurgical centres, and attention is centred mainly on the most suitable way of achieving this The most widely practised method is that of WEIRICH et al[8] in which the negative electrode is placed in the subcutaneous tissues or the muscles of the precordial region By means of voltages varying from 0 5 to 10, and currents of about 5 milliamps, pulses at the required rate, usually lasting not more than 2 milliseconds, can produce cardiac contraction at a pre-set rate, this being empirically determined by what is considered normal for the individual under given circumstances Such a method of stimulation usually works well, and the indications for stimulation are steadily increasing But long-continued stimulation of the heart[9]—for instance, in postoperative heart-block and in Stokes-Adams attacks—presents difficulties Infection along the electrode tracks cannot be warded off for ever Moreover the presence of electrically active foreign bodies in the myocardium eventually leads to fibrosis, and this in turn increases the electrical resistance of the tissues through which the current passes, consequently the stimulating voltages have to be gradually increased too And the need for a thoracotomy, and therefore for a thoracic surgical team, somewhat limits the availability of cardiac pacemaking

The myocardium can be stimulated through the intact skin by electrical induction,[10] or even by radiofrequency[11,12]—a development which spurs the imagination to the treatment of heart-block in outer space Both these methods, and also the implantation of transistorised miniature stimulating units[13,14] in the body wall, require preliminary thoracotomy—an operation of some magnitude in patients not usually very fit In this country WEALE[15] has shown that experimental pacemaking can satisfactorily be achieved by stimulating the ventricles by an electrode passed through a peripheral vein into the right ventricle, and FURMAN and ROBINSON[16] in the U S A have applied this method successfully to two patients By this means thoractomy and myocardial fibrosis are both circumvented—and electrodes are at all times exchangeable But, whereas the patient with an implanted transistorised pacemaker may be mobile and may theoretically need no attention for anything from four weeks[13] to ten years,[14] the patient with an electrode in the ventricles suffers some loss of mobility The introduction of an electrode into the myocardium via a cannula inserted through the chest wall[9,17] has the same drawback, and vigilance is needed to avert cardiac tamponade With implanted transistorised pacemakers, stimulating voltages cannot be increased when electrical resistance has risen, and the patient should probably not stray too far from medical supervision

Attempts to correlate the rate of ventricular stimulation with changing physiological demands, such as standing or exercise, have led to the experimental introduction of pacemakers " triggered "[18] by the electrical changes in the atria, which in heart-block have no chance of influencing ventricular rate and, indirectly, cardiac output The P wave can be monitored from either the atrial surfaces or the cavities As with untriggered pacemakers, both the transthoracic[19] and the venous-catheter[20] techniques are being explored It cannot be long before their clinical application will be reported, though evaluation of the advantages of " triggered " pacemakers over the ones at present in use promises to be a cardiological nicety It is claimed that " triggering " may increase cardiac output by some 15%—a figure conceivably of important marginal value

MCMILLAN[2] has shown that ventricular fibrillation is best treated by thoracotomy, not only because defibrillating apparatus is designed only for intrathoracic use, but also because sometimes ventricular fibrillation cannot be distinguished from asystolic arrest unless the heart is rapidly exposed to the surgeon's eye[21] This operation has a success-rate of only 24% under operating-theatre conditions, and, outside the operating-theatre, " penknife " thoracotomy has yielded a most discouraging success-rate[6] When facilities for observation are exceptionally good—for example, when the patient is being observed electrocardiographically[22]—the situation is somewhat different Here defibrillation may be achieved by a catheter electrode,[1 15] or by direct cardiac puncture of the ventricular cavity and the passage of defibrillating shocks through an insulated needle with a bare tip Provided such equipment is kept ready, a therapeutic test need take only a few seconds before thoracotomy and intermittent manual compression are initiated

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Asystolic arrest is thus the remaining hurdle WOODWARD[23] has found that sometimes the heart-beat is restored by immediately elevating the limbs, which fills the arrested heart with blood, but the main method of treatment is still direct manual compression coupled with intracardiac injection of adrenaline or calcium chloride

Iron-retention Diseases

HÆMOCHROMATOSIS in the form of "bronzed diabetes" is well known, though uncommon, in Europe and America It is thought to be caused by slightly increased absorption of dietary iron, amounting to about 3–5 mg daily throughout life[24] In South Africa excessive iron in the tissues of the Bantu population was first noted some years ago, and examination of tissues from patients who had died in hospital or accidentally suggested that the prevalence of such siderosis lies between 40% and 88% The amounts of iron have varied from a slight excess to a deposition as severe as in idiopathic hæmochromatosis This state of affairs has been explained in two different ways J and T GILLMAN[25] considered that the siderosis was caused by a widespread metabolic defect associated with chronic malnutrition, whereas WALKER and ARVIDSSON[26] believed that it was caused by excessive iron intake, because the Bantu cook their food and prepare their beer in iron cooking-vessels The two schools also differed about the pathological changes in the liver The GILLMANS thought that iron was first deposited in the liver cells themselves, whereas WALKER's group thought the reticuloendothelial cells were first involved BOTHWELL and BRADLOW[27] have reinvestigated this problem by examining tissue from Bantus who had died accidentally, they studied the histopathological changes in the liver and, in some cases, the spleen, and they estimated the amount of iron in the tissues

BOTHWELL and BRADLOW studied the livers of 147 patients and the spleens of 50, most of the patients were aged 20–50, and only 16 were females The iron concentration in the liver exceeded the normal maximum of 0 1% in all except 16, and the concentration tended to rise with age, reaching a maximum at 40–50 when the average iron concentration was as much as 1 10% Some degree of siderosis of the liver was found in 89 , of the patients, in 59% it was mild (i e , not more th 1 0%, which is a concentration of the same order as th in idiopathic hæmochromatosis) Histological studies showed quite clearly that the hæmosiderin granules were deposited first in the liver cells, and appeared in the Kupffer reticuloendothelial cells only when th higher concentrations of iron were present Portal fibrosis developed only when the iron concentration was really high, of 40 subjects with iron concentrations between 0 50 and 1 99% only 8 had mild portal fibrosis, and in 1 it was assessed as moderate But the 11 patients with iron concentrations above 2% all had portal fibrosis, in 2 this was mild, in 5 moderate, and in 2 severe, in 2 there was frank cirrhosis Investigation of the spleens showed that the iron concentrations paralleled those in the liver

These results support the opinion of the GILLMANS, which is linked with the observation that a similar distribution of iron in the liver is found in animals fed on deficient diets with considerable added iron[28] The appearances are quite different from those caused by iron accumulations following hæmolysis or infection, in these circumstances it is the reticuloendothelial cells that take up most of the iron[29] But BOTHWELL and BRADLOW cite an investigation which suggests that the diet of the Bantu in Johannesburg, though not optimal, is not in fact gravely deficient in any of the main constituents and is certainly not comparable to the laboratory animals' diet of uncooked corn meal Among the Bantu iron intake is undoubtedly excessive, often exceeding 100 mg a day, and the average serum iron level in Bantu males is about twice that in white males On the other hand, it has proved very difficult to produce cirrhosis of the liver in animals by overloading the tissues with iron, and since recent investigations and the features of idiopathic hæmochromatosis suggest that portal fibrosis depends on the iron exceeding a minimum concentration, some additional factor must be needed Chronic malnutrition does not seem to be a sufficient explanation, nor does variation in the ratio of iron and phosphorus in the diet A different explanation has been proposed by GOLBERG and SMITH[30]

When rats are given excessive amounts of iron by parenteral injection, iron accumulates in the liver and other tissues, but no hepatic cirrhosis is found even after so large a stretch of a rat's life as two years GOLBERG and SMITH found that when such iron overloading was combined with oral administration of the antimetabolite DL-ethionine, or with a diet poor in protein and vitamin E, hepatic cirrhosis appeared within a few weeks They think that the mechanism of the siderosis is "primarily one of excessive iron binding in the liver, from which the increased intestinal absorption follows secondarily" And they point out that in these conditions, unassociated with hæmolysis or marrow aplasia, the common factor is "actual or potential liver damage, the latter taking the form of

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22 B[illegible] C H[illegible] M Tay[illegible] D G [illegible] 19[illegible] p 191

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28 Gillman T Hathorn M Canham P A B [illegible]

29 [illegible] 19[illegible] 4 111

30 Golberg L Smith J P Amer J [illegible] 19[illegible] 36 12[illegible]

disordered metabolism of the hepatic cell" They suggest that such liver damage involves the excessive production of an iron-binding material which they call "haptosiderin", and which may be similar to the copper-binding polypeptide isolated from the liver in Wilson's disease This explanation would reconcile the hypotheses of GILLMAN and of WALKER and their co-workers since the disordered hepatic metabolism postulated by GILLMAN would be responsible for the excessive iron uptake from the undue amount of iron in the diet noted by WALKER GOLBERG and SMITH believe that the low protein content of the Bantu diet may be the responsible factor, the survey in Johannesburg indicated that the average daily intake of animal protein was 25 g and of vegetable protein 39 g, which is certainly less than the usually recommended daily minimum of 80–100 g protein Other deficiencies may be revealed by further work on this syndrome

Annotations

DIURETICS

THE observations that the sulphonamides were potentially diuretic [1] eventually led to the production of potent diuretics such as the chlorothiazides Their widespread use in the past two years or so has underlined their value in the management of œdema and has also enhanced our understanding of kidney function These advances in knowledge have been assembled in a special issue of *Chemotherapia* [2] in honour of the recent Basle International Congress of Internal Medicine at which œdema was discussed

The benzothiadiazine group of diuretics probably affect sodium excretion in the proximal tubule and potassium excretion in the distal tubule, and some support for this is afforded by the studies of Darmady and of Gaunt et al [3] on the selective localisation of radioactive hydrochlorothiazide in these areas The mechanism of tubular interference is ill-understood, but the effect on sodium and potassium excretion determines their main advantage and disadvantage To displace the prototype, new diuretics acting in this manner should be expected to cause increased sodium excretion with diminished potassium excretion Thus far, none of the growing family of chlorothiazide analogues has a significant advantage, instead, commercial competition has led to such small refinements as the incorporation of potassium, but the dose of potassium chosen by the pharmaceutical company may be too small When long-term diuretic therapy is necessary, and particularly when the underlying cause of œdema is hepatic cirrhosis, adequate oral potassium supplements are essential This is effectively and palatably administered in an effervescent tablet containing potassium bicarbonate, potassium acid tartrate, and anhydrous citric acid, as devised by Hadgraft [4] at the Royal Free Hospital Each tablet contains about 6 5 mEq of potassium and is equivalent to 0 5 g of potassium chloride, a dose of 8 tablets daily is recommended for cirrhotic patients on a low-sodium diet [5] Hypokalæmia is but one of the undesirable consequences of effective diuretic therapy, others include hypochloræmic alkalosis, low serum-electrolytes, hyperuricæmia, hyperglycæmia, and rashes and thrombocytopenia [6] The development of hyperglycæmia and glycosuria due to these sulphonamide-type diuretics is somewhat unexpected since another family of sulphonamides has precisely the opposite effect Goldner et al [7] have shown that this complication is restricted to diabetics and prediabetics

When œdema is associated with hyperaldosteronism, administration of the aldosterone-antagonising steroid, spironolactone, has a potent diuretic effect by acting on the distal tubule The use of spironolactone together with chlorothiazide has proved a synergistic combination in cirrhotic patients with ascites resistant to either diuretic alone [8] Shaldon [9] has reviewed his experience of the management of fluid retention in 51 cirrhotic patients in the past eighteen months, in which spironolactone has been available for clinical trial 33 (65%) patients responded to a low-sodium diet and either a mercurial or chlorothiazide-type diuretic, and 18 (35%) also needed spironolactone Only 4 (8%) patients had no satisfactory diuresis, and these subsequently died of liver failure His recommended diuretic regimen for patients with hepatic cirrhosis is initially rigid dietary salt restriction and bed rest, if this is insufficient one of the chlorothiazides and potassium are given If thiazide therapy has not produced satisfactory diuresis in a week, spironolactone is added and potassium supplements are reduced Satisfactory diuresis usually starts within three days and continues at a slow steady rate Uninterrupted combined diuretic therapy may be necessary for some months to eliminate ascites, and thereafter it is continued indefinitely Finally, if the patient fails to respond to this combination, it may be worth administering an osmotic diuretic—intravenous mannitol—in an effort to initiate diuresis This carefully planned regimen has virtually eliminated resistant ascites, repeated abdominal paracenteses, and the use of Southey's tubes, but close supervision is imperative if electrolyte disturbances and hepatic coma are to be avoided

Since the choice of diuretic was last discussed in these columns,[10] spironolactone, which then appeared promising, has become freely available and its value has been firmly established Its widespread and indiscriminate use may, however, lead to some disappointing results and to criticism of its lack of efficacy in certain œdematous states This can be expected if aldosterone antagonists are administered where œdema is principally due to factors other than hyperaldosteronism Some patients with congestive cardiac failure, for instance, do not secrete aldosterone in excess [11], and it has been suggested that urinary aldosterone levels are normal in "left-sided" heart-failure whereas they are elevated in "right-sided" heart-failure [12] Spironolactone will be used more rationally when a technique has been devised for detecting more readily cases with hyperaldosteronism

To this means of peripheral blockade of aldosterone are now being added central inhibitors of aldosterone secretion One such substance—methbipyrapone or SU4885—selectively inhibits the 11β-hydroxylation of steroids in the adrenal cortex, and so reduces secretion of the three main corticoids—aldosterone, corticosterone, and cortisol.[3, 13] Liddle[14] observed no significant differences between this central inhibitor of aldosterone secretion and a peripherally acting spirolactone in the urinary output of sodium and potassium in a healthy subject maintained on a constant high-sodium diet and prednisolone. On p. 1330 of this issue, Dr. Shaldon and Miss McLaren report their preliminary observations of the use of the hydrochloride of methbipyrapone—metopirone (Su-8874)—also a central inhibitor of aldosterone secretion, in 2 cirrhotic patients. Both had longstanding ascites which had proved resistant to various conventional treatments. Metopirone alone caused slightly increased urinary sodium levels in 1 but not in the other, and the clinical state of both patients remained unchanged. The addition of chlorothiazide promoted diuresis, indicating that it behaves synergistically with metopirone (a central inhibitor) as well as with spironolactone (a peripheral antagonist of aldosterone). On theoretical grounds, it could be predicted that spironolactone would be ineffective if aldosterone production were being blocked by metopirone, and Shaldon and McLaren do not explain why they used this seemingly incompatible mixture. Nonetheless, spironolactone was added to the combination of metopirone and chlorothiazide with quite dramatic and unexpected potentiation of sodium diuresis. But perhaps even more important are the theoretical implications of these findings. The 11-desoxycorticoid precursor of aldosterone has not yet been isolated, but if it accumulates as a result of metopirone blockade, then possibly it is antagonised by spironolactone. Although some of its properties can be surmised according to this hypothesis, the next essential step is to endeavour to isolate it.

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[12] Wolff, H P, Koczorek, K R. Buchborn E *Lancet*, 1957, ii 63

THE OXFORD CLINICAL SCHOOL

IN its Michaelmas number, the *Oxford Medical School Gazette* (always a lively publication) has a symposium on the future of the Oxford clinical school. This shows again the difficulty of breaking a tradition—in this case the tradition that the Oxford preclinical student leaves the rarefied atmosphere of Oxford for "a little Smithfield Market atmosphere, or the like". In writing of the present problems of the school the five Nuffield professors suggest that the biggest difficulty is that there are not enough students and that their calibre is not high enough. This difficulty has persisted even though the school, which is already well established in graduate teaching and research, offers the student excellent facilities—facilities so good, indeed, that the Goodenough Committee suggested that its role should be to turn out consultants, investigators, and teachers. The professors believe not only in what they can give to the students but also in what the students can give to them, and they find unthinkable any suggestion that the whole scheme should be abandoned—after so much money and effort have been invested in it.

The number of clinical students from Oxford would increase if the Oxford preclinical teachers did not remain, for the most part, ignorant of what goes on in the teaching hospital some quarter of a mile from their laboratories. And the number of clinical students from elsewhere might increase if the Oxford clinical school advertised more skilfully in other preclinical schools—not excluding Cambridge. But the difficulty of finding the right candidates for medicine is something which all face alike. Most teachers agree that, of their more talented science pupils, the proportion choosing a medical career is now lower than in the years immediately after the war. The propaganda of *Ward 10* may encourage patients to entrust themselves to our care, but will hardly induce clever young men and women to become doctors. If some of the medical information given through television, sound broadcasting, newspapers, popular lectures, and the like could emphasise not only the human side of medicine but also the scientific satisfaction to be derived from it, then more of the most able minds might be attracted to the profession.

WATER

To judge from his report for 1959 Dr. I. Gordon, medical officer of health for Ilford, would have found himself among kindred souls at the recent UNESCO conference on the problems of the arid lands. The borough draws its water partly from the Metropolitan Water Board and partly from the South Essex Water Company. Even in 1959 the first gave almost all that was asked, but the supplies from the latter were at times so insufficient that even the school privies could not be flushed. No-one seems to have died of thirst, but 25 gallons per head per diem is not really enough. The S.E.W.C. does not expect much improvement for several years. It has some large engineering projects in hand, but the amount of water which it draws from the M.W.B. cannot be increased until 1968 and it is still uncertain whether it will get permission to abstract more water from an unnamed river. (Essex is not so rich in purling brooks as to make this puzzle very difficult.) The M.O.H. is cross (and we do not blame him for it) because the S.E.W.C. did not foresee the shortage, has no representative of his authority on its board, provides no annual report, and seems to have rather old-fashioned ideas on public relations. The privately owned statutory water companies are some of the most efficient utilities in the land, but efficiency at any level is no excuse for failing to win the public confidence. Those who enjoy a monopoly must take the lead in exorcising the popular image of a suffering "we" and an omnipotent "they".

The fundamental worry of all suppliers of water in the London basin is that it is one of the driest parts of England and for more than sixty years the level of the water table in the surrounding chalk has been falling. The M.W.B. makes up its supplies from springs and wells in Hertfordshire and Kent and by drawing on the Thames. The S.E.W.C. serves a less favoured area without any great river and must do its best in a country notorious for brackish waters. At the same time the demand continues to increase. There are not only more people but also more bathrooms. Industry is insatiable, and we are sure the time has come when some more pressure should be put on the more lavish users to find ways either of saving water or of re-using it after purification. Rationing by price has failed. Some thirsty businesses, such as breweries, draw from their own artesian wells, but this water comes from the same strata that supply the general public. The industrial lust for more and more water is not limited to London, and even in such places as Wales (where most visitors find water in excess) it has caused alarm and grief. Another class of users who have troubled some smaller undertakings are the dairy farmers who often, for reasons which are almost forgotten, enjoy a supply either at a fixed

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13. C[illegible] W. S. Jr., Island, D., S[illegible] M., Lidd[illegible] G. W. J. c[illegible] [illegible] 19[illegible] 3[illegible] 2101.
14. Liddle, G. W. in The Clinical Use of Aldosterone Antagonists; edited by F. C. Bartter. [illegible] 1960.

rate or free An ample supply of clean water is a sine-qua-non for dairying, but, having only two hands, the busy farmer sometimes finds turning off the tap beyond his powers Lastly there are those—especially in suburban districts—who wish to wash their cars and water their gardens, and for these Dr Gordon seems to have a soft spot We wish that we could share his sympathy, but doubt whether this class of user got much attention at the UNESCO conference

We owe the beginnings of our admirable supplies of potable water to the sanitary awakening in the middle of the last century Clean water meant freedom from typhoid, dysentery, and cholera, and this is still the main reason for its supply Many industrial processes call for clean water, but relatively few for water of potable quality If the difficulties of supply forbid a separation of " clean " and " potable " we can at least value the latter at its proper worth as one of the buttresses of our public health When water is short we would encourage any water undertaking anywhere to forbid the use of its valuable product on the cabbage patches and to enforce this ruling with all its powers Any number of waterbutts can be filled from the roof, and the real enthusiast can dig his own well—as many cottagers have done and some still do And, if the gardener is too lazy for these measures, let him grow only those plants which will stand the drought as his fellows in less humid climates have done for centuries Then the children in Ilford will be able to flush the privies

FALLOUT IN AIR AND BONE

As far as we know, no-one has fired a high-yield nuclear weapon for over two years, and this commendable omission is probably reflected in new details [1] of radioactive fallout in air and rain Airborne particulate radioactivity in and around this country has been sampled for some years in the lower stratosphere, in the troposphere, and at ground level, and samples of rainwater are collected at two stations for analysis of radioactivity The data show that concentrations in air and rain of long-lived fission-product activity reached a maximum in 1959 and have since decreased significantly How much radioactive debris thrown up by weapon testing has still to come down? Working from observations on deposition and published data on stratospheric injection, Pierson et al [1] estimate that of a total injection of between 51 and 66 megatons equivalent fission yield, between 25 and 40 megatons remained in the stratosphere at the beginning of 1959 And about 11 megatons came down during 1959 If fallout is a simple exponential matter, these estimates point to a " common " half-residence time of one to two years—much less than was at one time supposed The stratospheric reservoir may thus be empty quite soon

New assays [2] of radioactive strontium in human bone in the United Kingdom in 1959 show some further increase for stillborn infants and children under 5, but in the second half of the year there was relatively little change compared with the first six months For the whole of 1959 the average level of ^{90}Sr in bone samples from children under 5 was 3 05 μμC per g of calcium (in 1958 it was 1 4) The highest single value in 1959 was 9 5 and the lowest 0 4 For adult bones the average radioactive strontium content remained a little over 0 1 The new monitoring report [2] which gives these figures records measurements made at the Woolwich Outstation of the Atomic Energy Research Establishment and in Glasgow and Cambridge, but it includes no comment on the significance of the results That will come in the Medical Research Council's second report on radiation hazards, to be published soon

INTERTERRITORIAL MEDICINE

Dec 1 was notable for surgeons and gynæcologists in West Africa, for on that day the West African Association of Surgeons came into being and its constitution was agreed at the inaugural meeting held at University College Hospital, Ibadan This was attended by 37 West African doctors who are practising surgery—1 from Sierra Leone, 3 from Ghana, and the remainder from Nigeria At the opening ceremony they were welcomed by the Governor of Western Nigeria, Sir Adesoji Aderemi, the Oni of Ife Sir Samuel Manuwa took the chair and was later elected the first president of the Association At the scientific sessions, continuing till Dec 5, ten papers were read, cases were demonstrated, and a morning was occupied with operations by the hospital staff The Premier of Western Nigeria, Chief the Hon S L Akintola, held a reception for the Association, and he was also the main speaker at its first dinner The Association of Surgeons of Great Britain and Ireland, and the corresponding Association in East Africa, were represented at the meeting The West African Association of Surgeons is the first interterritorial body of specialists in this part of the world, and its successful start is encouraging

INAUGURAL REPORT

THE Wolfson Foundation, which was set up in 1955 with the general aims of advancing education and health in the United Kingdom and Commonwealth, has published a report [1] of its first five years The first three were sensibly spent in assembling an efficient administrative machine and in exploring needs, and the actual work did not begin till July, 1958 But even in this restricted period over £3,300,000 has been distributed Of this sum almost £1,300,000 went to medical projects Some of the grants given for new buildings include £450,000 to provide the Royal College of Physicians of London with a larger home with more scope, £250,000 to build the Westminster Hospital a modern school of nursing, £150,000 to the Postgraduate Medical School of London for the Wolfson Institute, which will ultimately house not only lecture theatres and common rooms, but also library, museum, and laboratories, and £184,000 to the Institute of Psychiatry at the Maudsley Hospital to build lecture theatres and common rooms as the first instalment of a larger scheme

Another series of grants has gone to help research The British Empire Cancer Campaign is to receive £150,000 over ten years, and requests for apparatus and equipment will be met from this Wolfson fund It has already provided a mobaltron unit to St Thomas's Hospital, a new cobalt source to the theratron unit at Mount Vernon Hospital, and four climatic chambers for the Edinburgh animal supply and research unit Support to individual workers includes a fellowship to Mr A M H Bennett for his studies on the application of stereotaxic techniques in cerebral surgery, and a grant to Mr Wylie McKissock for anatomical and biochemical investigations of cerebral hæmorrhage Medicine will also benefit from many of the Trust's educational benefactions The work of the new institute and chair of criminology, for instance, will cover medical and social aspects of criminal behaviour, and the new university halls of residence in London and Glasgow will doubtless shelter some medical students from the harsh realities of lodging-house life

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[1] Pierson D H Crooks R. N Fisher E M R. Radioactive Fallout in Air and Rain AERE R3358 H M Stationery Office 7*s*

[2] Medical Research Council Monitoring Report Series no 1 Assay of Strontium 90 in Human Bone in the United Kingdom H M Stationery Office Pp 18 1*s* 6*d*

[1] The Wolfson Foundation Report 1955–60 Obtainable from the director of the Trust Lieut.-General Sir Harold Redman 20 Copthall Avenue London Wall E C 2

NEW RESPIRATORY VIRUSES

RESPIRATORY infections are the commonest cause of disease, disability, and death in this country The Newcastle upon Tyne survey[1] has again demonstrated the importance of these infections in children under 5 years In the U S A a study of 10 "healthy" young adults showed that in nine months each had on average 7 discrete minor illnesses, mostly involving the upper respiratory tract[2] Strides have been made in determining the viral ætiology of those infections not due to bacteria New myxoviruses (para-influenza types 1, 2, and 3) have been discovered,[3] and the role of the adenoviruses[4] has been clearly shown on an earlier page of this issue Mr Bell and his colleagues describe an outbreak resembling pharyngoconjunctivitis which was associated with type-3 adenovirus There is also one other new myxovirus —S A[5]—that may cause respiratory disease in man Sabin[6] has described a new group—the reoviruses —some of which cause such disease[7] Members of the enterovirus family also cause respiratory disease, and Coe[8] virus and the newly isolated common-cold viruses[9] may prove to be members of this family, just as the JH[10] and 2060[11] viruses probably are In 1944 Eaton et al[12] described the isolation of a virus from patients with primary atypical pneumonia and cold agglutinins This finding proved difficult to confirm, and it has become evident that some outbreaks of this disease are due to *Rickettsia burneti* and that others are probably due to adenovirus infections, but in 1957 Liu[13] triumphantly vindicated Eaton's early work by reisolating the virus and demonstrating its presence in infected chick embryos by the fluorescent-antibody technique[14] There is also another virus, originally called chimpanzee coryza agent but also called respiratory syncytial agent,[15] which is so far not classified[16]

This virus has been shown to cause disease in man[17] but has not proved easy to isolate Nevertheless Beem et al[18] have isolated it from 21 of a group of 46 patients, aged 0–6 months, with respiratory illness They used HEp 2 cells for isolation, but their success almost certainly derives from the fact that the cultures were inoculated only 1–3 hours after the specimens were collected Specimens were not frozen, and it was subsequently found that this virus is particularly susceptible to freezing and thawing One cycle reduced the titre, and storage at −30°C (with slow freezing) for five days destroyed the infectivity of a sample with a titre of 10^{-5} T C D$_{50}$ Virus could, on the other hand, be stored satisfactorily at −50°C after being rapidly frozen at −70°C Specimens that had yielded a respiratory syncytial virus were frozen and thawed three times to destroy this virus and were reinoculated into tissue cultures, but no additional isolations were made

The study was performed on two groups of children (inpatients and outpatients), and in each group children with respiratory illness and controls were examined Of 83 inpatients 27 yielded the virus, whereas of 42 controls none did Similarly, of 85 outpatients 11 had the virus in their throats, whereas of 81 control children none did The virus was usually isolated early in the disease Of 23 patients tested, 16 showed a rise in complement-fixation and 14 a rise in neutralising-antibody titre in convalescence Most of the infants in whom antibodies did not develop were under 6 months of age Bacteriological studies failed to reveal any difference in flora between virus-positive and virus-negative cases, except that *Hæmophilus influenzæ* was isolated four times as often from virus-negative cases

From this study it seems that respiratory syncytial virus was an important cause of respiratory illness in Chicago in the winter of 1958–59

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[1] Miller F J W Court S D M Walton W S Knox, E G Growing up in Newcastle upon Tyne London 1960 See *Lancet* 1960 i 865

[2] McNamara M J Thomas J H Strobl A, Kilbourne E D *Amer Rev resp Dis* 1960 82, 469

[3] Andrewes C H *Brit med Bull* 1959 15 221

[4] Huebner R J Rowe W P Chanock R M *Ann Rev Microbiol* 1958 12 49

[5] Schultz E W Habel K *J Immunol* 1959 82, 274

[6] Sabin A B *Science*, 1959 130 1387

[7] Rosen L Hovis J F Mastrota F M Bell, J A, Huebner R J *Amer J Hyg* 1960 71 266

[8] Lennette E H Fox V L Schmidt N J, Culver J O *Ibid* 1958, 68 272

[9] Tyrrell D A J Bynoe M L Hitchcock G Pereira H G Andrewes C H *Lancet* 1960 i 235

[10] Price W H *Proc nat Acad Sci, Wash* 1956 42, 892

[11] Mogabgab W J Pelon W *Ann N Y Acad Sci* 1957 67 403

[12] Eaton M D Meiklejohn G van Herick W *J exp Med* 1944 79 649

[13] Liu C *Ibid* 1957 106 455

[14] Coons A H Kaplan M H *Ibid* 1950 91 1

[15] Morris J A Blount R E Jr Savage R E *Proc Soc exp Biol, N Y* 1956 92 544

[16] Chanock R M Roizman B Myers R *Amer J Hyg* 1957 66 281

[17] Chanock R M Finberg L *Ibid* p 291

[18] Beem M Wright F H Hamre D Egerer R Oehme M *New Engl J Med* 1960 263 523

MORTUARIES

Medicine, Science, and the Law, the official journal of the British Academy of Forensic Science, has got away to a good start, and, judged by the first issue,[1] it will interest many besides members of the Academy

This issue includes a paper by H A Sissons, delivered at the first annual meeting of the Academy, in which he demands rethinking about public mortuaries He supports this demand by citing a letter from the Widdicombe File[2] and recounting the difficulties, and indeed dangers, confronting those who work in these places In hospitals it may be necessary only to remind the clinicians of the teachings of Semmelweis, but in public mortuaries the operator has no sure target for his plaint The coroner, for whom he is working, has no direct control over any mortuary and may adopt the attitude that some other person will do the work without grumbling The local authority, which provides and staffs the mortuary, is reluctant to spend money, unnecessarily as it seems Sissons recommends centralisation to make worth while the provision of proper facilities—a suggestion that will be widely supported All necropsies, including those undertaken to satisfy some apparently trivial legal consideration, should be carried out with the aim of advancing knowledge This aim cannot be pursued where indifferent operators work in unsuitable surroundings

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[1] *Medicine, Science and the Law* October 1960 1 edited by F E Camps To be published quarterly by Sweet & Maxwell Ltd 11 New Fetter Lane London E C 4 Subscription to non-members of the Academy 3 guineas per annum 17s 6d per issue

[2] *Lancet*, 1960 ii 1081

Dr J D S Cameron has been elected president of the Royal College of Physicians of Edinburgh

Special Articles

BRITAIN AND AMERICA[*]

Some North Atlantic Surgical Views

FRANCIS D. MOORE
M.D. Harvard

MOSELEY PROFESSOR OF SURGERY, HARVARD MEDICAL SCHOOL,
SURGEON-IN-CHIEF, PETER BENT BRIGHAM HOSPITAL, BOSTON, MASS.

TRAVELOGUES on the " American scene " have been a constant feature of British literature since the days of Captain John Smith. Since the war, there has been a resurgent outpouring of articles dealing particularly with surgery, medicine, and medical education.[†] To the American reader many of the features of American surgery that seem so inexplicable to the British visitor are to be explained by the differences between our two countries relative to the demand—the market—for the educational end-product: the young surgeon now ready to undertake the most expert practice, and a university post in teaching and research.

In the United States there are many communities, built within the past fifteen years, that do not have a well-organised medical establishment. In many cases they have a severe dearth of doctors and no hospital. These are not communities in the high hill coves of eastern Kentucky, where long-boned hillbilly riflemen sit around a wooden shack whittling on a stick. These are suburban communities of modern so-called " ranch-type " dwellings that embody the proverbial American standards of plenty: two chickens in every pot and two Cadillacs—or at least Volkswagens—in every garage. Many of these new communities are in the west, but they are not confined to the west. On Long Island, and in the suburban areas of Philadelphia, Baltimore, and Boston, one finds whole new developments of 10,000 to 50,000 people that have been built up where there was nothing before the war, and where any sort of medical establishment must be created out of whole cloth, or the small existing ones expanded tremendously.

It is a notorious fact—often dwelt upon by British commentators—that many surgical operations in America are done by people who are not surgeons by training or education. It is easy to assign this fact to lack of organisation, to lack of proper control and licensing, or to unvarnished avarice. Doubtless it is true that a certain fiscal attraction is revealed by the scalpel blade, yet even such self-seeking does not fully account for the American diffusion of surgical work, as one can readily satisfy oneself by making rounds at many community hospitals. There simply are not enough highly educated surgeons to go around. A study by Dr. Fred Coller (1957) showed that in some States almost 30% of the operations were performed either by general practitioners or by osteopaths. This is why there is such an urgency about our need for more medical schools and our concern over the postgraduate residency system.

In each hospital the residency system—or registrarship roster—must be as large as possible within the limit imposed by the need for each resident to have adequate personal experience. Today there are almost 15,000 Americans in residency training. This number is close to 10% of the total number of physicians who devote themselves to the care of the sick. Phrased another way, a large fraction of the American medical profession is clad in white suits, living in hospitals, receiving hopelessly inadequate fiscal support, providing care to the population—and all in the name of education.

As a result of this " seller's market " the young American surgeon finishing his residency at a good institution will have five or six attractive jobs lined up for consideration by the time he completes his hospital work. These positions may range all the way from a private group practice to an assistant professorship in a university department with opportunities for teaching and research at one of the new medical schools.

Contrast this now with the situation in Britain. A young man with a good surgical education seems to have to wait for someone else to move along before he can obtain a foothold as a consultant. According to one interpreter of the National Health Service, the need for more consultants is there but simply cannot be met because of the rigid tables of organisation set up by the N.H.S. in the teaching hospitals.

A further contrast here is of interest. I know of one of your urban teaching hospitals in which there is a surgical capacity of 140 beds. To take care of these patients there are six staff surgeons. The Brigham Hospital, in which our department is located, also has about 140 surgical beds. We have approximately twenty-five staff surgeons looking after these patients. One might say that we are overstaffed, although the balance seems to be a healthy one and gives men time to devote to teaching and investigation. There can be no question at all but that the British hospital in this instance is seriously understaffed. All six of the staff members feel this very keenly since they have but little time to deal with aspects of surgery other than operative care.

Regarding the wait for consultant posts in England, one of your deans pointed out that the great majority of new medical graduates had to go into general practice, and added: " Although the holding of a junior registrarship should be of great advantage to anyone taking up general practice it will be unfortunate if general practitioners have to be recruited from the ranks of disappointed ' trainee consultants ' " (*British Medical Journal* 1950). This makes quite a contrast with the U.S.A. wherein the reverse trend is often sadly noticeable. An example is that of a man whose surgical training has been largely on the clinical side, who then finds himself in a position as chief of service at a veterans hospital or as assistant professor in some medical school wherein he wishes he knew much more about research and academic life than he actually does.

What is the reason for this difference? According to one explanation, many of the contrasts in surgical training and practice and in hospital organisation are traceable to the difference between a well-established stable population and economy in England and one that is undergoing very rapid expansion at this time in the United States. During decades when the British population was fairly stable, the number of doctors has grown at a steady rate, as is shown in the accompanying figure. Note that the slope of the curve as the number of doctors has increased

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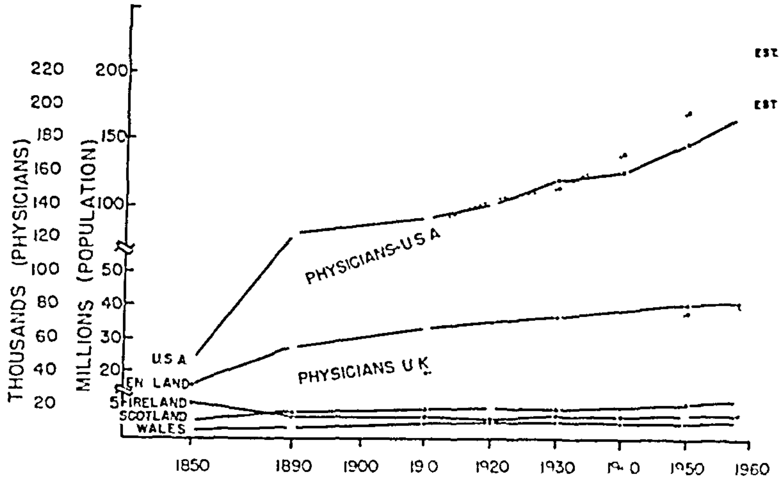
[*] Abstracted from the Moynihan annual lecture, University of Leeds, Sept. 24, 1959. This was the occasion of the 50th anniversary of the founding of the Moynihan Chirurgical Club.

[†] For reasons of length, the bibliography on transatlantic surgical visits cannot be published in full; it is available from the author.



Physicians and populations in the U.S.A. and in Great Britain and Ireland

in Great Britain and Ireland is almost identical with the slope of increase in the United States, where, by contrast, the population has grown significantly during this time. The increasing complexity of medicine has necessitated an increase in the ratio of doctors to population. This has occurred in England, but in America the change in ratio has been continuously retarded by an increase in population growth, resulting in career opportunities of an unprecedented sort.

Postgraduate Surgical Education and Surgical Habits

In the United States we are under pressure to produce a polished surgeon at the end of his residency years—one ready to take full responsibility in his community or medical school. In most well-organised institutions our residency system has a basic tenet that so far as possible long-term plans should be made for a man. The responsibility for the youthful surgeon must rest on one institution or be a joint responsibility between two or three institutions. The initial postgraduate commitment may be for three years, and if the resident does well he then goes on into the upper reaches of responsibility. His "chief" should remain loyal to his plans, helping to guide him through the vagaries of various clinical or research opportunities, and finally assisting him in getting a job. If the young man has any promise at all someone takes him under his wing and helps him plan.

At our hospital, as an example, the intern (house-surgeon) has a solid three-year commitment, and many of these go on to a six-year plan. One reaction of the British surgeon, on seeing such a system, is that it is stultifying, over-protective, surgical ‘momism" or even popism.’ ‘No one should stay at any hospital for that long a time.’ To which we would answer that these men do not remain in one hospital and that the system is therefore not stultifying. Indeed, at our hospital, again as an example, the residency involves two community hospitals and opportunities at three different urban teaching hospitals. In addition it involves, for those who wish to take it, a one-year fellowship in the laboratory or abroad. The man emerging from it is somewhat less qualified than one who has done nothing but clinical work.

As a visitor in Britain, I am impressed with the apparent success of a contrasting system in which the young man often takes a series of unrelated posts, commonly lasting no longer than six months at any one hospital and often involving a whole series of surgical sub-specialties before he has had general surgical operative responsibility. The Briton is apt to emphasise the length of American residency training, but for the young British surgeon who finally takes some sort of a consultancy post there has been just as long a period of education. And he is about the same age as his American counterpart. On both sides of the Atlantic the extreme extension of this training period, compounded by National Service, is a major problem.

There certainly is a pronounced difference in the degree of operative specialisation on the two sides of the Atlantic. The visiting British surgeon, travelling in America, often finds that, in his opinion, American surgeons tend to be too specialised. As one of them said: "You don't vary your work at all, you just do one field of surgery—something in the belly or something in the head—or else you don't operate at all." The Briton is apt to say: "*In America you only have specialists, in Britain we have general surgeons.*"

There may be some truth in all this, but the visitor is prone to overlook the fact that the American surgeon, while he may be moderately specialised in what he does in the operating-room (especially if it is a feature of his own research), is apt to be a "jack-of-all-trades" and seriously over-extended scientifically in his approach to the biological sciences that underlie surgery or to other aspects of surgery with which he is concerned.

The British surgeon operates in a variety of different pathological settings and organ environments, but frequently his operations and their related visits constitute his entire clinical life. So, when the visitor states that the Americans are too specialised, he should realise that in their totality of activity through a week or a month, they may be much less specialised than their British counterparts.

Differences between the two countries, *in surgical technique*, have often been described. I do not think they are very impressive. Patients on both sides of the Atlantic seem to get along surprisingly well! In general the American surgeon makes a bit more fuss over the details of asepsis and is apt to be shocked by the apparently casual approach in Britain. None the less, we have our full share of the 20th-century hospital plague. We also maintain a physiological chart of the anæsthetised patient while you rarely do—an omission that often impresses us as dangerous. The Briton is much more apt to pride himself on speed than is the American surgeon. There are doubtless some American surgical habits that are unnecessarily slow. Certainly some British surgical traditions emphasise speed to the exclusion of other more worth-while objectives. Detailed methods of securing hæmostasis in open dissections are surely in contrast, but both are effective.

The differences in the objectives of the residency system have a lot to do with some of the minor differences in operative procedure. The Briton coming to America states that he is aghast to see someone taking more than an hour to do a subtotal gastrectomy. Returning home he blames it on the Halstedian system: everyone spends all their time clamping little bleeders and frittering around in the operating-room." But this visitor often overlooks the fact that the man who is doing the gastrectomy may well be an assistant resident, doing his first or second case, and that, most important of all, the postoperative course of the patient is very smooth.

On the other side of the coin, we are surprised to see senior British surgeons spending a lot of their time carrying out operations on patients whose operative care we would supervise but leave in the hands of the residents. If the professor of surgery at Leland Stanford, the University of Chicago, Johns Hopkins, or Harvard spent all his time operating on the ward service patients, he could not conduct a residency training programme, because no residents would want to work for him. But, more important, he would never get anything accomplished in the way of investigation. Here again the pressure of work placed on all of you by a rather rigid table of staff organisation seems impressive to us.

The American is somewhat more prone to be concerned over the details of metabolic management of his patient and seems to have more of a desire to penetrate deeply into responsibility for the overall welfare of the patient. The Briton, somewhat more hurried by a big operating-list, is apt to leave this responsibility to others. There may be a slight difference in philosophy here as to the content of surgery itself. Certainly the American trend is increasingly toward a unified view of surgery according to which all aspects of the care of the patient are the surgeon's responsibility. I have tried to phrase our view as follows (Moore 1959):

> "The surgeon employs any effective means to serve the patient best. In most instances these include an open dissection under anæsthesia, as a surgical operation, together with supportive measures based on an understanding of the patient's bodily processes in recovery . . . the responsibility of the surgeon extends into all areas of human biology so as to provide the wise and effective care which is ever the trademark of good surgery."

One of our seemingly insoluble problems is that of the so-called "vanishing ward patient." This phrase refers to the diminution in numbers of free or charity patients in our teaching hospitals, occasioned by the growth of voluntary-hospital and surgical-insurance plans. The alleged disappearance of this ward patient places the surgeon in a difficult moral and ethical posture when he undertakes to discharge his responsibilities for postgraduate education in relation to the care of people who are, after all, private patients. This problem is a very pressing one in some centres in the U.S.A.

The reasons for this vanishing ward patient can be summarised by stating that we do not have a National Health Service or anything that approaches it, and that the growth of voluntary prepayment insurance in a period of fiscal plenty places a progressively larger fraction of our hospital population in the private and semiprivate categories. For the young man starting out in practice, this is a part of the "land of opportunity." But for the teacher this is a real problem. Particularly is it a problem if he is trying to conduct a residency programme designed to make residents fully experienced—like Athena, fully clad from the head of some surgical Zeus. Various formulæ are being developed that permit the private surgical teaching hospital to address itself frankly to surgical care by residents for several categories of patients.

As travelling Americans not only are we surprised to see your professors and senior staff members carrying out the straightforward gastrectomies or colon resections on the ward service patients, but also we are quite envious of the volume of surgical problems that still present themselves on the wards for the care and study of the surgical staff, the registrars, and the students. Current economic trends in the United States, highly desirable in most other ways (being associated with "prosperity"), make surgical training progressively more difficult.

Most Americans who make any effort to penetrate into the administrative bureaucracy of the National Health Service are impressed with the honesty of local administration that makes it run as well as it does. American government tends to show its most seamy side in its smaller political units. It is in the city, town, and county governments that the worst grafting, racketeering, and misuse of political privilege occur. And it is in these same small local units that your National Health Service must sink or swim on the basis of the honesty of its administration and on the unbiased selection of the most competent individuals. I think I am stating accurately the sentiments of many of my countrymen when I state that the National Health Service, as you know it in England, simply could not or would not work in America because we are not set up governmentally or politically to operate a homogeneous system free of special privilege on the tremendous scale required, and with our varying local conditions.

Another interesting professional contrast between the two countries has been the growth of the great private clinics in America. No such institutions have grown up in the United Kingdom or on the Continent. The best known of these clinics are the Mayo Clinic, the Lahey Clinic, and the Cleveland or Crile Clinic. With these as prototypes, many others have sprung up over the country. In most if not all instances these clinics have been built around the professional skill, business acumen, and public-relations sense of a surgeon or surgeons. It has been the centripetal character of surgery that was responsible historically for the beginning of these clinics: one surgeon of outstanding skill in some field of work attracted referral patients from a very wide area. With occasional exceptions, these private clinics have been attended by a considerable degree of financial success, by dint of which foundations could later be established which gave these enterprises some of the aura of eleemosynary institutions. As a general rule, the most senior members of the staffs of these clinics receive somewhat less emolument than they bring into the clinic in fees, while some of the younger men find a better living than they could if they were in independent practice.

This development has seemed in some ways to be a feature of a growing country, and certainly the historically eminent position of the Mayo Clinic in relation to the great plains and the mountain West bears out such an interpretation. The surgical orientation of these clinics has always been predominantly clinical, with little emphasis on undergraduate teaching, and a considerably less emphasis on postgraduate teaching than has characterised the hospitals where the large charity teaching wards were maintained. For the British visitor who is used to seeing a very large "list" run off by each senior staff member each morning, the atmosphere at these clinics frequently appears more congenial to his past background than do the residents' operating-lists and the much more varied activity of the charity hospitals. As a site for the study of large numbers of surgical patients managed in a uniform manner the great private clinics are unsurpassed.

The Academic Tradition

The activities of the senior surgeons and surgical teachers on the two sides of the Atlantic Ocean constitute one of the most fascinating differences between the two countries. Sir Heneage Ogilvie (1948) expressed some interesting ideas when he wrote his chapter entitled "American Surgery" in his book *Surgery, Orthodox and Heterodox*. He had some ideas about Americans that might be classified as amateur anthropology of the Captain John Smith variety. But he did perceive that the American tends to fill his day to a degree that appears pathological, compulsive, neurotic, and quite hopeless. He writes: "The American Surgeon does work like hell—and then some. One whom I have visited at length gets up at 5 every morning, goes to bed at 9, and while at work takes no part in social activity." This certainly seems to be a sad existence, and one can only commiserate with this lack of social activity on the part of Ogilvie's anonymous host, whoever he was.

Why does the professor or senior surgeon work so hard at so many different things? Is it a local sign of the national neurosis? Well, it could be so classified, but it also arises from the fact that one cannot conduct an effective teaching surgical service without at the same time conducting a many-faceted organisation that includes personal participation in research, raising funds for men, construction, and research, and lending a hand in various local and national organisations.

Somehow, we feel that your departments—though they may have less money available for research—secure these funds with less "fuss and feathers", and spend them more efficiently. On the other hand, we are often impressed when visiting large and important surgical departments in the United Kingdom to find that the professor, while a fine clinical surgeon, has little interest in the study of the biological issues of surgical illness, at least as manifested by his own record of research.

The American experience has tended to show that an individual who never has done any research at all (and who therefore has no personal knowledge of the difficulties of trying to ferret out information from Mother Nature by the methods of Claude Bernard) can scarcely be expected to head or conduct a good research programme. He can hire people to do the work, and he may occasionally hire the right person and get some good work done. But, in general, even his own hirelings will find him difficult to deal with when they come with specific requests or with specific plans that he fails to appreciate because of lack of experience—much as the physician fails to appreciate the technical problems of a difficult duodenum merely because he has never dug one out of the pancreas.

With some background experience in research, an individual can foster a reasonably well-balanced research activity in a department, even though he himself can participate in only a small amount of it. It is of egregious importance that he indeed does participate personally with his own two hands, both to maintain his running contact with research and as an earnest of his own interest and motivation. The day of the "research executive" has happily not yet arrived in surgery. This personal participation in the laboratory adds a facet to the weekly activity of the American surgeon of the university hospital—a facet that is often not viewed and is but little appreciated by the visitor.

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Thus, some of our professorial swarm of activity—"what makes the surgeon run?"—has to do with these things as well as the more familiar aspects of the residency programme, operating, rounds, lectures, and that great institution so well explored on both sides of the Atlantic—The Committee.

A final point that I would like to discuss, having to do with the "American scene", is the interesting fact that we are sprouting new medical schools at a fairly brisk rate. Since 1930 ten new medical schools have been founded and six schools that have had two-year programmes previously have now developed four-year curricula. Many with part-time clinical teachers are going over to the full-time. This has created a minimum of seventeen new professorial positions in surgery that did not previously exist, and at least a hundred and fifty new top-rank teaching positions in surgery and the surgical specialties.

No young surgeon would expect himself to be considered for a position of responsibility in any one of these new schools if he himself did not know his way around in some field of biological science. He must know both the concepts and the techniques of some advancing field. It is not just a matter of publishing a few papers. He must be a "self-feeder" in terms of investigative ideas. It is not enough to be a good surgeon and a good lecturer. He has also to show himself to be productive. The research fields involved may be as diverse as cerebrospinal-fluid dynamics, renal function, open-heart techniques, hypothermia, or something deeply rooted in the biophysical sciences, such as studies of coagulation, wound healing, calcification, or endocrinology. This allegedly high standard for professorial appointments is satisfactory enough to contemplate in the abstract. But when one comes to the detailed matter of eighty-five medical schools and half a dozen of them opened in the past four years, one suddenly realises that we are getting into a situation where the demand for such people hopelessly outstrips the supply.

Conclusion

Most of the contrasts on two sides of the North Atlantic are minor, but several are of major interest, and all are basic to understanding of surgery in the two countries.

We have unsolved problems in many areas in which you have found very happy solutions, while in other areas we have developed trends peculiar to our own population and economy, some of which seem quite healthy. There is unquestionably a tremendous opportunity in the United States, both in university surgery and in community practice. Although the frontier officially closed when the last hostile Indian bit the dust, the population growth of the past two decades has created impressive new frontiers of medical need. Many of the contrasts are due to this difference in population-growth rate in the recent past.

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LABELLING OF PRESCRIBED MEDICINES

THE following statement has been issued by the Joint Formulary Committee.

There is considerable support for a suggestion that when prescriptions are dispensed, the label of the container should always carry the name of the preparation or drug in order that the contents may be readily identified. It is contended that this would enable a doctor called in to treat the patient of a colleague, when no record of treatment was readily available, to tell at a glance what had been prescribed. It is also claimed that this would provide important safeguards against confusion by the patient where several preparations are concurrently prescribed, and would prevent, for instance, the wrong tablets being taken in error. On the other hand, it has been argued that disclosure of the contents would encourage self-medication with potentially dangerous preparations, for the patient may not appreciate that on another occasion the same symptoms are not necessarily due to the same cause and that a surplus of medicine previously prescribed may neither be any longer active nor suitable treatment. Furthermore, containers are fragile and patients have been known to keep several kinds of tablet in one box.

The Joint Formulary Committee, representing the medical and pharmaceutical professions has considered this proposal very carefully. It is the duty of the pharmacist to carry out faithfully the exact instructions regarding labelling which are written by the prescriber. It is clearly the duty of the prescriber to decide whether it is in the best interests of his patient that the name of the drug or preparation should appear on the label of the container. The Joint Formulary Committee believes that prescribers are already aware of the advantages of readily identifying the nature of medicines that are prescribed, and wishes to take this opportunity of reminding prescribers that this can be done quite easily.

If it is the wish of the prescriber that the identity of the preparation should appear on the label, he should include with the directions for use on the prescription the desired name or description of the drug. For example:

Label (Sig.) { Phenobarbitone Tablets
(strength if required)
One to be taken twice daily

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In the absence of these specific instructions the conventional label would read:

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Public Health

LEAD POISONING FROM HOME-MADE WINE

T. P. WHITEHEAD
F.R.I.C.

A. P. PRIOR
M.B. Sydney

From South Warwickshire Hospital Group Laboratory, Warwick

DURING this century, lead poisoning has become a rare disease. Occasionally, however, cases do occur as a result of ingestion of lead from bizarre sources. These have included lead nipple-shields, toys, paint, crayons, batteries burned on domestic fires, and even the lead in the print of newspaper used as toilet paper.

Our case of severe lead poisoning was the result of drinking home-made wine.

Case-report

A village butcher, aged 52, was admitted to hospital in November, 1958, on account of abdominal pain of three weeks' duration. The pain was a dull ache in the epigastrium and, although worse on some days, it could not be described as abdominal colic, it was unrelated to food and unrelieved by alkalis. The liver was palpable two fingerbreadths below the right costal margin. Radiological examination of the alimentary canal was normal.

Hæmatological investigation showed a sedimentation-rate of 65 mm. in the first hour (Westergren), and a hæmoglobin of 8·1 g. per 100 ml. The red cells were well hæmoglobinised, and showed polychromasia and basophilic stippling. A tentative diagnosis of lead poisoning was made, and urinary lead determination on two consecutive days showed increased excretion, 0·31 and 0·40 mg. per day. Normally urinary lead excretion is below 0·2 mg. per day.

Questioning the patient about his work, hobbies, and diet revealed no obvious source of lead, but he admitted he was an enthusiastic maker and drinker of home-made wine. He had been doing this for twenty years and had remained well until the past few weeks. He argued strongly that there was no possibility of lead contamination of his wine, and his friends drank as much of it as he did.

The patient asked to be discharged over the Christmas period and we took the opportunity of having various items of diet investigated, including the well water at his home and the beer at his pub, all with negative results. A public health inspector had a look at his wine-making equipment, but there did not appear to be anything unusual in the process, nor was there any obvious source of lead.

Early in January, the patient had an epileptic fit, was readmitted to hospital, and promptly had another. An electroencephalogram showed intermittent bursts of irregular spike activity in both hemispheres. Investigation showed that the anæmia and basophilic stippling of the red cells were still present. Urinary lead determination showed excretion of 0·75 mg. and 1·0 mg. on two consecutive days. Coproporphyrins were present on qualitative examination. We now felt certain of the diagnosis of lead poisoning and the patient

URINARY EXCRETION OF LEAD DURING TREATMENT WITH EDATHAMIL CALCIUM-DISODIUM

Day	Edathamil (g. per day)	Urinary excretion of lead (mg. per day)
1		0·75
2		1·00
3	3	9
4	3	17
5	3	9
6	3	9
7–9		
10	3	7
11	3	11
12	3	9
13	3	
21		0·46
22		0·38

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2		1·00
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11	3	11
12	3	9
13	3	
21		0 46
22		0 38

was treated with edathamil calcium-disodium (calcium disodium versenate). This was given intravenously (3 g. per day) in two periods of four days with a three-day break between them. The table shows the resultant urinary excretion of lead. This reached a peak of 17 mg. per day on the second day, and the average excretion during the first four days of treatment was 11 mg. per day. Average excretion of urinary lead during the second four-day period was 9 mg. per day.

With renewed enthusiasm we attempted to show the source of lead. A sample of the patient's home-made elderberry wine was obtained. This was of a rich, red colour and had a not unpleasing bouquet. It had a slightly metallic after-taste, which was scarcely surprising as it contained 7·5 mg. of lead per litre. Without doubt it was the vehicle of administration.

The wine was made by soaking ripe elderberries in a muslin bag in an earthenware vessel, known as a jowl (fig. 1). After forty-eight hours, the liquor was tipped into an electric wash-boiler. Here sugar was added and the liquor boiled before being transferred back into the jowl. Yeast was added and the liquid allowed to ferment. When this had reached a satisfactory stage, the liquor was decanted into two earthenware barrels in which it was stored.

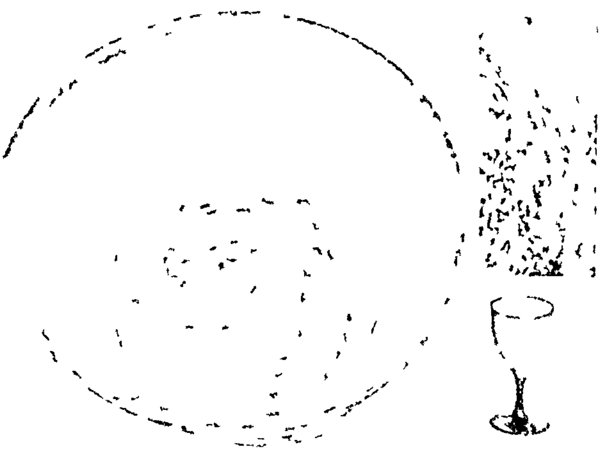

Fig. 1—The jowl used in wine making.

Fig. 2 (inset)—Close up of the glaze of the jowl showing the pitted surface.

To ascertain the source of lead, a litre of hot 1% hydrochloric acid was put into each of the containers used in the process, and the lead content of the resultant solutions was found to be:

Vessel	*Lead content (mg. per litre)*
Boiler	8
Jowl	1000
Earthenware storage jar (A)	9
,, ,, (B)	7

The earthenware jowl yielded 1000 mg. of lead, and was thus the source of the lead in the wine. With the aid of the British Ceramic Research Association, we ascertained that the jowl was over a hundred years old and was a relic of the age when such containers were glazed with soft lead glazes. The glaze was cracked and pitted (fig. 2) by the acidity of the wine, and pieces of the glaze were even finding their way into the wineglass.

Our patient did, in fact, consume about two pints of the wine a week. The presence of discrete particles of glaze would make it difficult to know precisely the amount of lead consumed before clinical symptoms appeared. He had used this container for the first time in 1958 and had inherited it from an aunt. The container had a local reputation for the flavour and potency of the wine produced in it.

The patient is now well and has a normal urinary lead excretion; his hæmoglobin level and red-cell appearances are normal.

Discussion

Fermented liquors as a source of lead in lead poisoning have a long history. In 1772, Sir George Baker showed that Devonshire colic was due to lead contamination from lead-lined cider presses—and was then denounced from the pulpit as a faithless son of Devon.

During the 19th century in Austria, it was the custom in many country places to put a piece of lead into the wine barrels because the superfluous acid was supposed to be absorbed by the metal and the wine thus improved. This resulted in saleable wine but in many cases of lead poisoning.

Lead contamination of cider from the lead glaze of earthenware storage-jars was mentioned in 1909 (*Lancet* 1909) as a possible explanation of lead poisoning in Dorset.

Masters (1919) investigated earthenware containers used for culinary purposes and showed that, when they were used for storing or cooking food containing malic or citric acids, these plumbosolvent acids could lead to serious contamination of the foodstuffs with lead.

The soft lead glazing of earthenware vessels was a very hazardous process for the pottery workers concerned, and, after the Lancet Commission on Some Leadless Glazes (1899), leadless glazes were adopted and cases of lead poisoning decreased considerably. The Commission was formed to protect workers in the pottery industry. Its valuable work not only saved many lives, but also probably much illness.

It has been stated that there are more than half a million people in this country who brew home-made wines. We were informed that more than three hundred gallons were stored in the various houses in the village in which our patient lived. We have determined the lead content of a number of different samples of home-made wine made and stored in earthenware jars and have found them free from lead.

Lead-glazed containers are probably still used by some home brewers, but the lead contamination is not appreciable until the glaze becomes cracked and broken.

Books which give hints on the preparation of wine in the home have been known to suggest junk-shops as a source of suitable equipment. But antique earthenware should be avoided, and containers with cracked and pitted glazes should be discarded.

Summary

A case of severe lead poisoning is described. The patient was successfully treated with edathamil calcium-disodium (calcium disodium versenate). The source of lead was the glaze of an earthenware container used in making wine in his home.

Our thanks are due to Dr. Stephen Whittaker under whose care the patient was admitted.

We are grateful to the Director and staff of the British Ceramic Research Association for help in the investigation of the glazes of the earthenware vessels used by the patient.

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In England Now

A Running Commentary by Peripatetic Correspondents

Now that we are reconsidering the details of our medical course we feel that we should take every opportunity of giving our students a wide knowledge of the interrelationships of medicine and modern society. A conducted tour of the local brewery is an accepted feature of the class in microbiology in many medical schools, but here we can go one better, for we are on excellent terms, not only with the local brewery, but also with one of the local vignerons, and our enthusiastic microbiologist has already inserted tours of both establishments into the syllabus. On each the exposition is followed by a judicious sampling of the products in rooms thoughtfully provided for the purpose. Only by field-work of this kind, it is felt, will the students acquire a proper respect for the name of Pasteur and an understanding of the basic importance of microbiology. Not only this, but our socially conscious professor of medicine considers it vital that the students should gain some insight into the problems of alcoholism, and feels that this might best be provided by a second visit to the vineyards—a visit on which the conversation would take a very different turn though the final sampling procedure would be almost identical.

Now the surgeons, in their bluff way, would like to take their tutorial classes along for a historical chat on the use of wine as a surgical antiseptic, and even our pathologist thinks he would find it convenient to expound upon cirrhosis surrounded by a supply of the causative agent. In such an atmosphere we have been forced to meditate on the possibility of making use of these unrivalled facilities for the benefit of preclinical students. It has been urged, for example, that our lectures on the mechanisms of swallowing might be supplemented by practical work in the field, or that a class on reaction-times could be profitably arranged. We ourselves see no need to advance such specious arguments, for we well remember an educational experience we had some years ago, when the medical society of which we were then a member invited a director of a wine firm to guide us through a small selection of his wares.

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Now, obviously, if Mendelism doesn't work in the realm of pure mathematics it won't work for sweet peas, or blood-pressure, or piebald and skewbald horses, or anything else in biology. I'm terribly sorry, but I'm afraid I've upset the whole basis of modern genetics. Perhaps, however, it will now be possible to reconcile Professors Platt and Pickering since the whole business of genetics is clearly nonsense.

Of course, some smart Alec will say "he's forgotten the prime numbers." Since prime numbers are, by definition, odd numbers we must remove them from our series from 1 to 100 first. I've done this and the ratio is still not what it ought to be—1 : 3. Try it and see.

* * *

Recent advances in the study of chromosomes must not blind us to the fact that a great deal of much more fundamental work must have been done on the quiet in America. An embryologically minded colleague, back from the United States, informs us that in a clothing store he observed a cupboard labelled on one side "Boys' Genes", and on the other "Girls' Genes."

* * *

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I went to a film on the Royal Ballet. We saw extracts from *Swan Lake* and *Firebird*. It wasn't bad but I wouldn't go again.'

was treated with edathamil calcium-disodium (calcium disodium versenate) This was given intravenously (3 g per day) in two periods of four days with a three-day break between them. The table shows the resultant urinary excretion of lead Thus reached a peak of 17 mg per day on the second day, and the average excretion during the first four days of treatment was 11 mg per day Average excretion of urinary lead during the second four-day period was 9 mg per day

With renewed enthusiasm we attempted to show the source of lead A sample of the patient's home-made elderberry wine was obtained This was of a rich, red colour and had a not unpleasing bouquet It had a slightly metallic after-taste, which was scarcely surprising as it contained 7 5 mg of lead per litre Without doubt it was the vehicle of administration

The wine was made by soaking ripe elderberries in a muslin bag in an earthenware vessel, known as a jowl (fig 1) After forty-eight hours, the liquor was tipped into an electric wash-boiler Here sugar was added and the liquor boiled before being transferred back into the jowl Yeast was added and the liquid allowed to ferment When this had reached a satisfactory stage, the liquor was decanted into two earthenware barrels in which it was stored

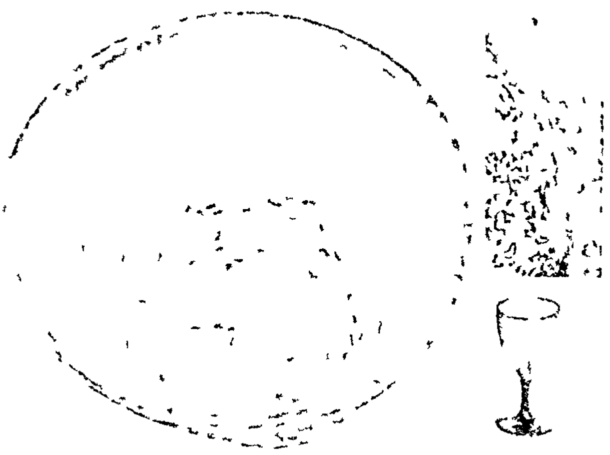

Fig 1—The jowl used in wine making

Fig 2 (inset)—Close-up of the glaze of the jowl showing the pitted surface

To ascertain the source of lead, a litre of hot 1% hydrochloric acid was put into each of the containers used in the process, and the lead content of the resultant solutions was found to be

Vessel	*Lead content (mg per litre)*
Boiler	8
Jowl	1000
Earthenware storage-jar (A)	9
,, ,, (B)	7

The earthenware jowl yielded 1000 mg of lead, and was thus the source of the lead in the wine With the aid of the British Ceramic Research Association, we ascertained that the jowl was over a hundred years old and was a relic of the age when such containers were glazed with soft lead glazes The glaze was cracked and pitted (fig 2) by the acidity of the wine, and pieces of the glaze were even finding their way into the wineglass

Our patient did, in fact, consume about two pints of the wine a week The presence of discrete particles of glaze would make it difficult to know precisely the amount of lead consumed before clinical symptoms appeared He had used this container for the first time in 1958, and had inherited it from an aunt The container had a local reputation for the flavour and potency of the wine produced in it

The patient is now well and has a normal urinary lead excretion, his hæmoglobin level and red-cell appearances are normal

Discussion

Fermented liquors as a source of lead in lead poisoning have a long history In 1772, Sir George Baker showed that Devonshire colic was due to lead contamination from lead-lined cider presses—and was then denounced from the pulpit as a faithless son of Devon

During the 19th century in Austria, it was the custom in many country places to put a piece of lead into the wine barrels because the superfluous acid was supposed to be absorbed by the metal and the wine thus improved This resulted in saleable wine but in many cases of lead poisoning

Lead contamination of cider from the lead glaze of earthenware storage-jars was mentioned in 1909 (*Lancet* 1909) as a possible explanation of lead poisoning in Dorset

Masters (1919) investigated earthenware containers used for culinary purposes and showed that, when they were used for storing or cooking food containing malic or citric acids, these plumbosolvent acids could lead to serious contamination of the foodstuffs with lead

The soft lead glazing of earthenware vessels was a very hazardous process for the pottery workers concerned, and, after the Lancet Commission on Some Leadless Glazes (1899), leadless glazes were adopted and cases of lead poisoning decreased considerably The Commission was formed to protect workers in the pottery industry Its valuable work not only saved many lives, but also probably much illness

It has been stated that there are more than half a million people in this country who brew home-made wines We were informed that more than three hundred gallons were stored in the various houses in the village in which our patient lived We have determined the lead content of a number of different samples of home-made wine made and stored in earthenware jars and have found them free from lead

Lead-glazed containers are probably still used by some home brewers, but the lead contamination is not appreciable until the glaze becomes cracked and broken

Books which give hints on the preparation of wine *in* the home have been known to suggest junk-shops as a source of suitable equipment But antique earthenware should be avoided, and containers with cracked and pitted glazes should be discarded

Summary

A case of severe lead poisoning is described The patient was successfully treated with edathamil calcium-disodium (calcium disodium versenate) The source of lead was the glaze of an earthenware container used in making wine in his home

Our thanks are due to Dr Stephen Whittaker under whose care the patient was admitted

We are grateful to the Director and staff of the British Ceramic Research Association for help in the investigation of the glazes of the earthenware vessels used by the patient

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Baker G (1772) *Med Trans Coll Physns*, 1, 175
Commission on Some Leadless Glazes (1899) *Lancet*, i, 4[illegible]
Lancet (1909) i, 6[illegible]5
Masters H (1919) *Lancet*, i 1092

In England Now

A Running Commentary by Peripatetic Correspondents

Now that we are reconsidering the details of our medical course we feel that we should take every opportunity of giving our students a wide knowledge of the interrelationships of medicine and modern society A conducted tour of the local brewery is an accepted feature of the class in microbiology in many medical schools, but here we can go one better, for we are on excellent terms, not only with the local brewery, but also with one of the local vignerons, and our enthusiastic microbiologist has already inserted tours of both establishments into the syllabus On each the exposition is followed by a judicious sampling of the products in rooms thoughtfully provided for the purpose Only by field-work of this kind, it is felt, will the students acquire a proper respect for the name of Pasteur and an understanding of the basic importance of microbiology Not only this, but our socially conscious professor of medicine considers it vital that the students should gain some insight into the problems of alcoholism, and feels that this might best be provided by a second visit to the vineyards—a visit on which the conversation would take a very different turn, though the final sampling procedure would be almost identical

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The wines were ranged in line on a white-covered table, with reinforcements underneath. The society gazed solemnly through the glasses at the guttering candles provided, it inhaled the aroma up the backs of its noses, and for the first three bottles or thereabouts it spat out the mouthfuls into a bucket in professional style But when it came to one it liked, the discipline broke down, and by the time it reached the sixth or seventh bottle it was drinking heartily Afterwards we were surprised to find that our ranking of the first four was identical with that of the society's impresario, though our vocabulary was not in his class For example, what we had said about the Chateauneuf-du-Pape 1947 was "alpha minus, taste good, colour good, smell good" What we should have said was "A noticeable burnt, roasted flavour, a very good glass of wine" Of the winner, a Corton 1928, our notes read "alpha, very pleasant" This, we found, was "A beautiful glass of wine, lacking the astringent pull of young wine Lovely smooth soft drinking, with a wonderful breeding and bouquet The finest drink on the slab" Of the Fleurie 1950, which was last in order of sampling, we had written, in handwriting by this time grown rather large and expansive "Undistinguished" Clearly we had begun to find our form, but what we had really meant was "A hard, unyielding, unforthcoming wine, a little harsh on the nose"

It seems obvious to us that an organised wine-tasting is in itself an excellent educative procedure to include in the preclinical curriculum. It would develop all those qualities which the clinicians find deficient in our students—their command of language, their powers of observation and description, and their capacity to synthesise information and come to a decision We are bringing the matter to the notice of the Faculty tomorrow

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'I went to a film on the Royal Ballet. We saw extracts from *Swan Lake* and *Firebird* It wasn t bad but I wouldn t go again.

Letters to the Editor

REFRIGERATED VENTILATION FOR OPERATING-THEATRES

SIR,—Your editorial review (Dec. 3) of the outstanding new book on *Hospital Infection* by Williams, Blowers, Garrod, and Shooter[1] wisely challenges certain points of view in this otherwise admirable work. I should like to reinforce your remarks about the need for refrigerated ventilation plant in operating-theatres. To say, as the authors do, that "in London, the daytime maximum temperature exceeds 77°F on an average of only twelve days of each year" is surely to *justify* and not to disprove the need for refrigeration plant.

Perhaps I may be permitted to illustrate this subject by reference to a newly completed theatre suite at St. Albans Hospital. There we have had the valuable advice and collaboration of Dr. Blowers himself on certain aspects of the ventilation system. From the strictly bacteriological point of view it may be said that the system is excellent. But, from the point of view of atmospheric conditions in the theatres during hot weather, our plant is both inadequate and dangerous. I hasten to add that Dr. Blowers is *in no way responsible for the faulty basic design imposed* on us by the Ministry of Health.

The past summer has been notable for its poor weather and generally low temperatures, and our experience with this unrefrigerated ventilating-plant is consequently all the more significant. On May 17, 1960, at 2 P.M. the atmospheric conditions outside the theatre suite were temperature 63°F and relative humidity 53%, within the theatres, 76°F and 82%. On May 31 the morning conditions within the theatres were 75°F and 77%. On June 5 the temperature in the theatres was 82°F (humidity not recorded because no wet-bulb thermometer was available). On June 17 (a rather "sticky" day) the outside temperature was 78°F and relative humidity 82% at 11 A.M., within the next six hours the temperature inside the theatres rose from 75°F to 86°F, and humidity from 90% to 95%. These admittedly selected samples from our records bear witness to the intolerable conditions which can be created by inadequate ventilation equipment of *this type even during a bad summer*.

The most important reason for giving publicity to this subject is to ensure that unrefrigerated ventilation plant is not installed in other theatre suites. Before the installation of the St. Albans plant, and acting on the advice of an independent consulting ventilation engineer, our surgical staff clearly warned the regional hospital board and the Ministry of Health of the inevitable consequences of their action. Despite that warning and repeated requests that the plant should be modified no effective action has been taken. If the Ministry of Health is waiting for more convincing factual evidence in the form of a corpse of a patient dead from heatstroke, then it seems possible that we may have to wait until next summer to provide it. In the meantime it is surely a pity that an excellent book by four such eminent bacteriologists should seem to lend authority to the wrong and thoroughly misguided views enunciated in the Ministry of Health Bulletin on operating-theatres.

[illegible] REGINALD S. MURLEY

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[1] Williams, R. E. O., Blowers, R., Garrod, L. P., Shooter, R. A. Hospital [illegible]

[2] [illegible] Operating Theatre S[illegible] [illegible]

ADMINISTRATION IN MENTAL HOSPITALS

SIR,—Dr. Bardon (Nov. 12) is bluffing when he implies that the tremendous opportunities for advance offered to mental hospitals by the Mental Health Act are lost by refusal to accept (his) basic principles of hospital administration.

In the first place, the Mental Health Act does not offer such opportunities, and, in the second place, medical superintendents at such hospitals as Dingleton, Netherne, Mapperley, and Warlingham Park made tremendous advances before the new Act without Dr. Bardon's recommendations.

Indeed, having served with Dr. Bardon on a medical advisory committee, I think he would be the first to agree with me that it was not his experience that the medical advisory committee was capable of agreeing on a common policy which they could implement. In fact it was the disagreement and perpetual stalemate that resulted in junior doctors innovating some of the advances that were made.

Furthermore, at that hospital all consultant psychiatrists had complete clinical control of their beds without interference from the medical superintendent, but did not themselves initiate any tremendous advances.

For these reasons I am puzzled that Dr. Bardon should recommend so strongly a system which his experience and the available evidence has shown to be inadequate, thus depriving psychiatric hospitals of positive leadership so urgently needed during the next few years.

I wonder if any medical advisory committee would have had the foresight and knowledge to produce policies such as open doors, unrestricted visiting, and all the other advances which have been made to control institutional neurosis in the past decade.

Theoretically a group of consultant psychiatrists and senior hospital medical officers mature in outlook, unbiased in judgment, widely read, and in touch with modern trends would be able to produce ideal working policies and implement them. Many who know, if they are really honest with themselves, what actually happens at medical advisory committee meetings would have to doubt if the petty and often personal squabbling that goes on would ever enable a policy to be produced, let alone implemented.

Senior administrative medical officers are acknowledged to be necessary to regional boards. A psychiatrist in charge of a department is thought to be necessary in a teaching hospital, and a chief medical officer is realised to be necessary at the Ministry of Health. It may be such systems of medical administration are mistaken, but I doubt it.

In psychiatric hospitals the situation is different. It is time somebody stated publicly (I had hoped somebody else would do so) *how incompetent many* consultants and S.H.M.O.s in psychiatry are, both in their work and in affairs generally. I do not think it would be fair to patients or to junior doctors in psychiatric hospitals to inflict one of these people as their director in the interests of democracy. It is not, I suspect, by chance or victimisation that merit awards in psychiatry are so much rarer than in other specialties. Nor is the attitude of physicians and surgeons to psychiatrists entirely due to the prejudice or the state of psychiatry as a science.

It may be that the medical director, superintendent *(call him what you will), should be elected by consultants, consultants should be elected by junior hospital staff, and perhaps qualification should be democratically bestowed by students or their fellows—it is doubtful. As I see it,* selection of the more industrious and capable psychiatrists for the role of chief-of-service or consultants by a panel of experts is a more satisfactory solution. Similarly in the case of matrons.

No one can deny that the position of medical superintendent has been abused and misused in the past, but, then so has the position of consultant psychiatrist. I have known junior doctors who bitterly resent doing most of the work in a mental hospital under the pretext of "being trained", while a consultant did very little and received four times the pay, together with miscellaneous privileges and status.

To me it seems contrary to the spirit of medicine that either a medical superintendent or consultant should continue indefinitely in office, regardless of his performance, professional competence, and industry. Practical solution is not easy but not impossible. Everyone cannot but agree that a system which prevents patients benefiting from the more competent administrations of some doctors in order that an incapable official is well paid is highly undesirable.

There can be no doubt that every psychiatrist should be free to do what he ought to do but not necessarily free to do what he likes. Until the evolution of some method of getting rid of those who are concerned with their rights but neglect their obligations, I submit it will be foolish of the Ministry or medical profession to be rattled any further by the disgruntled vociferous group who confuse the shortcomings of the personality of some medical superintendents with the system of administration of which they are part. A careful investigation into the contribution made to psychiatry by these individuals with a "thing" about authority would prove very interesting.

Severalls Hospital,
Colchester,
Essex.

RUSSELL BARTON.

SIR,—Dr. Kidd's letter of Dec. 3 marks a considerable advance on this subject. However, a point which I think has been insufficiently emphasised is the importance of medical staff committees as described in the Ministry of Health circular H.M.C. (53) 87. In many mental hospitals these committees have scarcely begun to function adequately. The old idea that the medical superintendent alone need be consulted lingers on, and the rest of the senior medical staff have no contact with the management committee.

The posts of chairman and secretary to the medical staff committee should rotate among the senior medical staff at least once every three years. Both these officers should have direct access to the chairman of the management committee at least once a month. Without some such procedure, it is not practicable for the medical staff to make their views known or be aware of hospital policy.

Littlemore Hospital,
Littlemore,
Oxford.

J. E. DUFFIELD.

SIR,—I am prepared to agree with Dr. Kidd that evolution is preferable to revolution but would suggest that there is nothing very revolutionary about asking that the relationship between management committees and medical staff in mental hospitals should be one of mutual respect and courtesy. I agree that the Mental Health Act has nothing to say about how a hospital is administered, nor did I say that it has. I did say that the Act offers mental hospitals tremendous opportunities to advance, and I suggest that one of the opportunities it offers is the evolution of the relationship between hospital management committees and medical staff mentioned above. Dr. Kidd (Oct. 29) clearly indicated that he believes that the presence of a medical superintendent in the administrative structure hinders this evolution by causing the hospital management committee "... to take more notice of his monthly reports than the resolutions of the medical advisory committee".

I will leave it to matrons, chief male nurses, and others to comment on Dr. Kidd's suggestion that it is part of the function of a medical superintendent "... to interfere in matters of administration and discipline of medical and nursing staff", and that he should be answerable for such interference, not to his medical and nursing colleagues, but to hospital management committees or regional hospital boards.

With regards to Dr. Kidd's suspicion "... that powerful unconscious motives may be at work" in determining the point of view of many clinical psychiatrists, I presume he would agree that the imputation or even the demonstration of motive behind a proposition does not make the proposition false.

Shenley Hospital,
near St. Albans,
Herts.

D. BARDON.

DEFERRED MITRAL VALVOTOMY
A CONTROLLED SURGICAL TRIAL

SIR,—Your annotation[1] reviewing retrospective studies of groups of patients with well-developed mitral stenosis, treated medically and surgically, leaves little doubt which is the correct treatment once a critical stage has been reached but, as you suggest, "it is doubtful whether the patient without symptoms or systemic embolism should be subjected to the operation as a prophylactic measure".

In an endeavour to remove this doubt, a controlled trial of early surgery versus conservative medical treatment in patients with established stenosis but few symptoms other than moderate breathlessness on exertion was started in Cardiff in 1955. The trial was never completed because fewer local cases were available than had been expected, and the climate of medical opinion moved away from early surgery whilst it was under way. Our experience is none the less relevant to current discussion of the problem.

In 1955 the ethical difficulty of allocation into two groups, for early surgery on the one hand or medical treatment and possibly deferred surgery on the other, was simplified for us by the existence of a waiting-list of patients; random allocation could therefore ethically be used to decide whether the patient would be recommended for immediate operation or deferred for a period under close medical supervision. In our experience medical criteria of suitability for inclusion in the trial can be fairly easily defined; the definition of surgical criteria is more difficult because the surgeons' willingness to operate also depends on the patients' attitude and willingness to undergo operation. In the Cardiff trial, cases were included on a random basis only after this consent had been freely given by patients considered potentially suitable for valvotomy in other respects.

Early operations were performed within two months. At six-month and twelve-month intervals all subjects were followed clinically and physiologically, the principal aim of the latter being to provide objective evidence of exercise tolerance and cardiopulmonary function during exercise. In the course of eighteen months, 23 apparently suitable cases in the age range 20–44 years were seen and referred, each to two medical referees. Of these, 9 were accepted for inclusion in the trial, 5 for early operation and 4 in the deferred operation group. During the succeeding four years, 1 of the deferred cases has come to operation and another has been excluded on account of anæmia. 1 of the cases operated on, a man aged 34, has had a recurrence of rheumatic fever.

The trial has been abandoned for the reasons mentioned, but we are of the opinion that this approach is still needed to discover the best method of treatment for those with few symptoms but definite signs. In view of Dr. Bannister's findings[2] it might now be considered reasonable to limit it, at least in the first instance, to those under the age of 10. But it is, one hopes, in this group that most of the new cases will be detected over the coming years.

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[1] Lancet, Oct. 1, 1960, p. 748.
[2] Bannister, R. G. ibid. Aug. 13, 1960, p. 329.

It is our impression that there is still considerable divergence of view between different centres on the correct treatment for early mitral stenosis, and as a result there is in effect an uncontrolled trial in progress in the country as a whole. It seems a pity that this divergence of view and uncertainty cannot be used to carry the knowledge of the correct treatment of mitral stenosis a stage nearer perfection.

M R C Pneumoconiosis Research Unit, Cardiff United Hospitals and Sully Hospital, Glamorgan

J E Cotes
Byron Evans
H M Foreman
J C Gilson
H R S Harley
P D Oldham
William Phillips
Harold Scarborough
Dillwyn Thomas
A J Thomas
L R West

SURGERY OF PAINFUL HIP

Sir,—During the past two years I have seen fifty cases of painful hip. In most of these, shortening of the gracilis muscle limited abduction, and caused a little flexion of the hip and (on lying flat on the back) of the knee. Most of these patients had been advised to have the hip replaced by a metal or plastic joint, or to have the hip-joint immobilised by pinning. Instead, I have divided the gracilis tendon near the pubes, and in all these cases this has stopped the pain and greatly increased the mobility.

The operations were carried out under local anæsthesia. The gracilis muscle is readily recognised because it has a shining tendinous sheath at its origin. (It is the only muscle in this region with such a sheath, and I wonder whether this tendinous sheath has anything to do with its shortening.) Before the tendon is divided, it should be injected with a local anæsthetic, because it is very tender. There are often fibres through the muscle, and these must be divided. In some cases the muscle should be cut right through: indeed I rather think that this is best in the majority. A drainage tube should always be inserted, and personally I always use 1/8000 perchloride of mercury throughout the operation, to prevent sepsis.

These patients did not have rheumatoid arthritis in the hands, wrists, elbows, or ankles, and I do not think that the painful hip was due to this condition. I operated on two cases of painful hip with rheumatoid arthritis in the wrists, hands, and elbows, and, though the pain was not entirely relieved, mobility was increased.

Sandhurst, Kent V Nesfield

MAGNESIUM SULPHATE IN THE TREATMENT OF CORONARY THROMBOSIS

Sir,—There is need in general practice for an alternative to anticoagulant therapy. Though its efficacy is well attested it has considerable drawbacks, quite apart from the nuisance of repeated blood-tests.

Phenindione therapy, for example, is not without complications, such as hepatitis,[1] drug fever, and neutropenia, and may have to be stopped because of unexpected hæmorrhage. It is unsuitable for patients with impaired liver function, peptic ulcer, &c. Even a dormant pile may be a contraindication, as in one of my early patients who became severely anæmic from this cause.

Within the past year another patient (with an apparently safe prothrombin level on the day of onset) had severe hæmaturia which persisted for two days despite repeated intravenous injections of vitamin K_1, another developed intractable epistaxis requiring blood-transfusion, and a third was unsuitable because the infarct complicated an operation for jaundice due to common-bile-duct obstruction. This experience may be unfortunate but I doubt if it is rare.

Even when therapy could be safely continued in hospital it had to be stopped on discharge because the patients were scattered over wide areas beyond laboratory control. For all these reasons I now resort to treatment with parenteral magnesium sulphate. This was first described in 1956 by Malkiel-Shapiro and his coworkers[3] in South Africa, with very favourable results, and similar results were obtained in Tasmania last year by Parsons et al.,[4] who wrote: "Over 100 patients suffering from coronary heart disease (of which at least one third were acute myocardial infarctions) were treated with intramuscular magnesium sulphate with only one death, while 196 cases of acute myocardial infarction treated with routine anticoagulants gave a 30% mortality."

Magnesium salts are known to protect rats against experimentally produced myocardial necroses[5] and endomyocardial fibrosis,[6] which provides a basis for the belief that they may be beneficial in man. It has been shown, too, that a correlation exists between serum-magnesium and serum-cholesterol levels in man,[7] which may have a bearing on coronary atherogenesis.

The simplicity of the treatment makes it eminently suitable for general practice especially in countries like this, and its apparent safety and effectiveness justify further trials. The 6 cases I have treated recently are too few for valid conclusions, and I should be grateful to know the results of any further large trials or whether any are contemplated.

Nakuru, Kenya A L Craddock

ORAL TREATMENT OF PERNICIOUS ANÆMIA WITH LOW DOSES OF H P P /1

Sir,—Dr Smith (Nov 19) is not strictly accurate when he refers to the correspondence between Dr Varadi and ourselves as an "argument", for we have expressed no opinion, as yet, on the significance of serum-B_{12} levels on H P P /1 therapy.

We have merely attempted to discover from Dr Varadi what scientific evidence he has for his conclusion that the serum level reflects the degree of intestinal absorption, on this form of therapy. Judging from his letter of Nov 19, his conclusion seems to be based on an experiment yet to be performed.

Dr Shinton too (Nov 5) speaks of the rational concept of restoring the serum-B_{12} level to normal, but unless the serum/tissue relationship is known on this form of therapy his statement is no more than a half-truth, and could, therefore, be misleading. Theoretically, one of three things could happen to a hæmopoietic agent after absorption from the gut—excluding loss from excretion. Firstly, it might be selectively absorbed from the serum by the tissues, thus giving a higher tissue than serum level of vitamin B_{12}. Secondly, the absorbed agent might become largely bound to the protein of the serum, thus giving a disproportionately high blood level as compared with that in the tissues. Thirdly, the hæmopoietic agent might be distributed equally after absorption, between serum and tissue.

In our opinion, until one knows which of the three possibilities actually occurs on H P P /1 therapy, there is no point whatsoever in attempting to draw any conclusions from the serum-vitamin-B_{12} concentrations alone. The danger in so doing is a serious risk of discrediting a highly acceptable hæmopoietic agent merely because the first of the three possibilities has occurred. Conversely, a relatively inactive preparation might yield disproportionately high serum-B_{12} levels because of binding to the serum proteins.

We agree, substantially, with the rest of what *Dr Smith* says in his letter. Certainly we think that, having established the clinical superiority of H P P /1 over oral crystalline B_{12}, the

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1. [illegible]
2. [illegible]
3. Malkiel-Shapiro, B, B[illegible], I, Terner, P [illegible] Med Pr[illegible] 19[illegible], [illegible] 4[illegible]
4. Pa[illegible], R S, B[illegible], T, S[illegible] [illegible] 19[illegible], ii, 4[illegible]7
5. Selye, H *Brit med J* 195[illegible], i, 5[illegible]
6. Selye, H *Lancet* 19[illegible], i, 13[illegible]
7. B[illegible], I, Oel[illegible] [illegible] 19[illegible], i, 10[illegible]

important thing now is to discover whether the treatment remains successful over a period of years We do not, however, share Dr Smith's belief that oral therapy will never supersede the parenteral treatment of pernicious anæmia, and we doubt whether his enthusiasm for securing vitamin B_{12} in two or three inches of muscle would be shared by most of his patients

St. Helens Hospital,
St. Helens Lancs

F S MOONEY
J G HEATHCOTE

"THEY NEVER TELL YOU ANYTHING"

SIR,—Even if there are difficulties with doctor-patient communication, need there be any with that of doctor-relative?

My mother was a hospital patient and up to her discharge the most I could ascertain was that she had undergone a major operation. The knowledge that I am a hospital administrator failed to loosen the shackles of silence I never saw the medical staff when I visited, which owing to distance was not very frequently, but surely the ward-sister is sufficiently responsible to impart some kind of information The fact that my mother is over 80 made the situation more absurd, or so it seemed to me.

Wembley

P E WINDO

PULMONARY EMPHYSEMA

SIR,—Dr Rappaport and Dr Mayer (Dec 3) have written a provocative article Some of their assertions demand close scrutiny because questions are raised which they do not attempt to answer

Early in their paper they dismiss the lung as "primarily an organ of motion" How else can one visualise it? Do they really believe that ventilation plays so small a part in the normal and disordered physiology of the lung?

"Chronic bronchiolitis and bronchitis of insidious origins" are not, according to Dr Rappaport and Dr Mayer, significant in the pathogenesis of emphysema Yet later in the paper they list as possible causes "the whole gamut of infections—allergic inflammations, and toxic (physical or chemical) agents which reach these structures either by the blood-stream or by inhalations (fine aerosols)" One fails to see the difference between these processes and that of chronic bronchiolitis and bronchitis

They also state that emphysema may be initiated by failure of "visceral function   non-functioning air spaces enlarged by *coalescence of alveoli* and kept open by thoracic traction become subject to mechanical enlargement by air trapping" The writers do not say by what process coalescence of alveoli takes place If they deny that these alveolar changes are secondary to bronchiolar dysfunction, what process do they envisage as causing alveolar coalescence with enlargement of the air sacs? In this context I would refer to the work of Krahl[1] Krahl installed an artificial ball-valve in the bronchus of a rat's lung which offered resistance to expiration and caused local inflammation in the airway After the valve had been in position for some time, the lungs distal to the valve showed grossly discernible distension of peripheral airways with tendency to collapse Microscopically there was '*degeneration of the alveolar septa with formation of abnormally large air spaces*" This important paper adds weight to the evidence that emphysema begins primarily as bronchial obstructive disease, and that the alveolar changes are not primary

Dr Rappaport and Dr Mayer are convinced that in some cases of emphysema no acquired disease is present, and in these cases postulate "pre-existing defects in the lungs of post-natal developmental origin' It would be of interest if the authors would explain just what is meant by this

Seemingly, they ascribe emphysema to a primary loss of visceral lung function, by which they mean loss of diffusion surface for the lung All the disorders of ventilation including changes in air flow, residual volume of air, and derangement of the mechanics of breathing, are dismissed as secondary effects following primary coalescence of the alveoli—a process which they totally fail to explain in terms of ætiology

Bearing in mind the observed clinical facts of the relationship of emphysema to bronchitis, either infective or chemical (smoking, air pollution, cadmium, &c), and in view of the experimental evidence described above, it is difficult to accept the explanation given in this article The loss of diffusion capacity may be explained as a *secondary* phenomenon following the loss of available diffusion surface This loss of diffusion surface is surely due to the breakdown of the alveolar septa, which in turn follows bronchiolar obstruction

Until Dr Rappaport and Dr Mayer provide additional evidence, their argument must surely remain theoretical and unproven

The London Hospital,
London, E.1

B H BASS

SHINGLES AND CHICKENPOX

SIR,—Having followed with interest the recent letters about zoster and chickenpox, may I cite a very up-to-date case, which bears out Colonel Foster's letter of Dec 3

A young man developed pain at the back of the neck on Nov 14 and a few macules two days later After another two days he had typical zoster of C2 and C3 On Nov 30 his 7-year-old daughter became "off colour" and on Dec 3 a typical chickenpox rash appeared There was no known contact of chickenpox, nor do I know of any local cases This works out as prodromata zoster to stated prodromata chickenpox 17 days, rash of zoster to rash of chickenpox 17 days

London, E.2

G LAWSON

PULMONARY HYPERTENSION

SIR,—Would Dr Goodwin and his colleagues (Oct 8) explain how they can diagnose "slight right ventricular hypertrophy" clinically—i e, at the bedside?

Moreover, is it possible to be certain that a second pulmonary sound is "narrowly split" when over the same area an ejection click and a systolic murmur are reputed to have been heard? In other words, the authors claim that with each heart-beat, a period of time which is less than one second, they can hear over a small area five different sounds, accurately identify them, and report on them each individually

Do many other of your readers claim to have these abilities, which, incidentally, are rivalled by another cardiologist who maintains that he often hears eight different sounds in the mitral area with each heart-beat and can identify accurately and report on each individually? Of course I do meet many postgraduate students who make similar claims but I do not take them seriously as they are very rarely successful in the M R C P clinical examination, because they fail to diagnose the very elementary heart cases which are shown

London W 1

M H PAPPWORTH

*** We showed this letter to Dr Goodwin, whose reply follows —ED L

SIR,—Slight right ventricular hypertrophy is diagnosed at the bedside by the presence of a diffuse tapping cardiac impulse felt to the left of the sternum, accompanied by a gentle lift of the sternum The normal left ventricular thrust may still be felt, but often the left ventricle is impalpable

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[1] Krahl V E *Amer Rev resp Dis* 1959 80 158

Normally the 2nd heart-sound is single on expiration but separates clearly on inspiration into its two components of aortic and pulmonary valve closure Narrow splitting indicates that this normal separation on inspiration is reduced in degree, and on quiet breathing the two components of the sound are closer to each other than normal Increased pressure in the pulmonary artery leads to more rapid apposition of the cusps of the pulmonary valve, which causes the sound component of the second heart-sound to occur earlier Narrow splitting is thus a useful sign of pulmonary hypertension, and is often accompanied by increase in intensity of the pulmonary component

The ejection click occurs in systole well before the second heart-sound, and the systolic murmur (which is due to ejection of blood under increased pressure through a dilated pulmonary artery) is heard as a longer, lower-pitched sound than the click, which is high-pitched and short

We feel that experienced auscultators will confirm our ability to detect in the same patient an ejection click, an ejection systolic murmur, and narrow splitting of the second heart-sound

These physical signs are not mere figments of the imagination, but are vital links in the chain of evidence which leads to the diagnosis of pulmonary hypertension For the inexperienced, they are not always easy signs to elicit, but their recognition at the bedside is most important, for they contribute to the detection of diseases which may be curable if treated early but which if undetected may prove fatal

Postgraduate Medical School,
London, W 12

J F GOODWIN

ANTICOAGULANT THERAPY

SIR,—I have been misquoted in your account (Dec 3, p 1247) of the symposium on anticoagulant therapy

In an attempt to estimate the requirement for long-term anticoagulant therapy, I obtained from 30 general practitioners, covering 70,000 of the population, the numbers of their patients (*a*) who had suffered a myocardial infarction within the two previous years and were still alive, and (*b*) who were suffering from angina of effort

From these figures 1% of the population require long-term anticoagulant therapy *not* 10% as stated in your report

University Department of Medicine,
Royal Infirmary Glasgow

A S DOUGLAS

A SUCKER FOR EMPTYING THE INTESTINE

SIR,—Mr Lawrie's account (Nov 19) of a sucker for evacuating the small intestine prompts this report of a cheap 'home'-made instrument

It is made from a suitable length of semirigid, medical-grade, thin-walled, polyethylene tubing Holes as required may be drilled with a dental burr, and the end plugged with polyethylene rod if considered necessary During sterilisation a metal or glass rod is placed inside the tube to preserve its straightness till it is cool again

It is connected to the sucker tube by a glass connection ('Vules cartridge') It may be extended in length by further pieces of tubing plus an extra glass connection

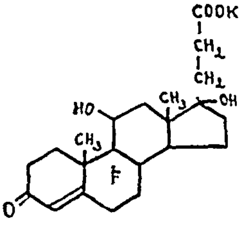
If necessary, this simple contraption may be made in several different diameters Its lightness is a very desirable attribute, and if necessary it can be bent

[illegible]

KEITH F D SWEETMAN

PROTECTION BY ANTI-MINERALOCORTICOID AGAINST AN OTHERWISE FATAL DIHYDROTACHYSTEROL INTOXICATION

SIR,—Spironolactone, an anti-mineralocorticoid, inhibits the otherwise fatal cardiac necroses that are produced in rats by pretreatment with fluorocortisol and subsequent exposure to the stress of restraint[1] Recently, Mr E A Brown, of G D Searle & Co, Chicago, Illinois, synthesised 'sc-11927', a much more potent anti-mineralocorticoid that is not a spirolactone but has the formula 3-oxo-9α-fluoro-11β, 17β-dihydroxy-17α-pregn-4-ene-21-carboxylic acid (potassium salt)



We found that this compound is even more active than spironolactone in blocking the cardiotoxic effect of fluorocortisol plus stress, and the question arose whether it could also inhibit the cardiovascular toxicity of compounds other than corticoids

50 female Holtzman rats, with a mean initial body-weight of 101 g (± 0 68 g), were subdivided into five equal groups and treated as shown in the accompanying table For the production of cardiovascular damage, the animals of all groups were treated with 35 µg dihydrotachysterol ('Calcamin') and 2 mmol $\mathrm{Na\ HPO_4}$ mixed together and administered by stomach tube, in 2 ml of water twice daily sc-11927 was given, at the doses in the table, in 0 2 ml of water subcutaneously twice daily The experiment was terminated on the 5th day by killing all survivors with chloroform Immediately after necropsy, hearts and kidneys were inspected with a binocular loupe, then fixed in neutral formalin for examination of sections stained with hæmatoxylin-phloxine and the v Kóssa

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Group	Dose of sc-11927 (µg)	Final body weight (g)	Cardiac lesions (scale 0–3)	Nephro calcinosis (scale 0–3)	Mortality
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II	5	98 ± 2 30	2 2 ± 0 41	2 7 ± 0 23	60 %
III	10	97 ± 2 51	1 8 ± 0 11	1 7 ± 0 37	60%
IV	100	117 ± 1 45	0	0	0
V	500	119 ± 2 90	0	0	0

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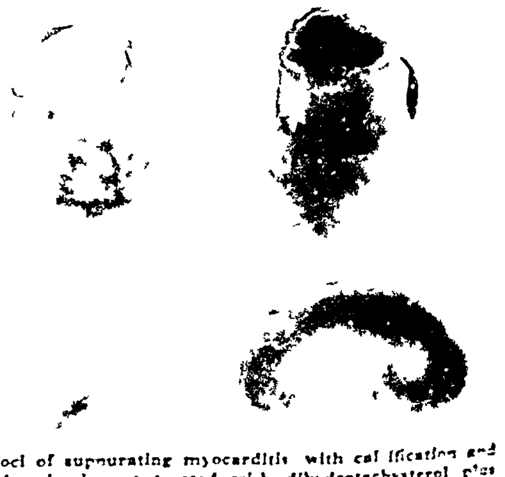
1 Selye, H *Proc Soc exp Biol, N Y* 1960 104, 212



Multiple foci of suppurating myocarditis with calcification and nephrosclerosis in rat treated with dihydrotachysterol plus Na_2HPO_4 (left) compared with corresponding essentially normal organs of a rat that received similar treatment but was protected by minimal effective dose (100 µg) of SC-11927 calcium stain The readings given in the table are the means (with standard errors) of macroscopically and microscopically observed organ lesions expressed in terms of an arbitrary scale of 0 (no lesion), 1 (slightest detectable lesion), 2 (moderate lesion), and 3 (most severe lesion)

All but 1 of the controls died, exhibiting even macroscopically evident lesions of suppurating myocarditis, with calcification of cardiac muscle and coronary arteries as well as pronounced nephrocalcinosis, as previously described.[2] SC-11927 proved to be virtually ineffective in doses of 5 and 10 µg Rats treated with 100 or 500 µg, however, were completely protected as regards loss of body-weight, cardiac lesions, nephrocalcinosis, and mortality

Two possible explanations of this protection should be considered

(1) Although SC-11927 is a potent anti-mineralocorticoid, it may have blocking actions against compounds other than corticoids, such as dihydrotachysterol

(2) The fatal cardiotoxic and nephrotoxic actions of dihydrotachysterol plus Na_2HPO_4 may depend upon the " conditioning " action of endogenous mineralocorticoids, if so, blockade of the latter would abolish the toxicity of the treatment administered

SC-11927 exhibits no detectable inherent toxicity per se when administered at ten times the prophylactic dose level, and even sudden intravenous injection of 2 5 mg of this compound produces no demonstrable damage Hence, further studies concerning the possible prophylactic actions of this anti-mineralocorticoid against lesions not primarily due to mineralocorticoid intoxication seems to hold promise [*]

This work was supported by grant No H-3688(C3) from the National Heart Institute, U S Public Health Service, and by a grant from the Gustavus and Louise Pfeiffer Research Foundation

H SELYE
S GRASSO
N PADMANABHAN

Institut de Médecine et de Chirurgie expérimentales Université de Montreal,
Montreal

RETIREMENT OF MEDICAL RESEARCH-WORKERS

SIR,—Nowadays medical research-workers usually retire at the age of 65 With a life of scientific discipline behind them, many could do useful work for some further years A few are snapped up by pharmaceutical firms with which they have had previous contact, a few go to W H O or to staff embryo Commonwealth medical schools, or are allowed a corner in a University laboratory, a group of elite who would otherwise have retired are producing first-class research in an institute near Cambridge These facts indicate sustained competence A large number, from inclination or for health reasons, probably wish genuinely to disengage A significant number, however, would like to work but are too diffident to mention this audibly influenced by old-age inferiority feelings, obsessed by forgetfulness of colleagues' names, and recalling their own impatience with clingers to office, they announce their joy in the prospect of time for gardening

On the hypothesis that a limited amount of facilities suitable for such people already exists or can easily be created—off the career ladders and therefore noncompetitive—I suggest a special employment agency for retired medical (perhaps also other) research-workers Applicants for full-time or part-time work would register It is important that not only the previous line of work be given, but also any private bents which, in a scientifically trained person, might attract a potential employer (I can call to mind an eminent organic chemist who was expert on insect ecology, a bacteriologist clever at scientific advertisement copy-writing, and so on)

The agency should be non-profit-making and academically sponsored And this leads to a special point in favour of my suggestion An initial and annual relevant medical examination should be a condition of acceptance of employment through the agency While primarily intended to avoid awkwardness, this provision would make available an opportunity for gerontological research on the performance of selected intellectuals Perhaps the N d Foundation would be interested?

For obvious reasons I sign myself merely

" AGED 60 "

IS RADIOLOGICAL EXAMINATION OF THE TWISTED ANKLE NECESSARY?

SIR,—I commend Dr Garfield's iconoclasm (Nov 26) in examining the desirability of X-raying every injured ankle

He is right when he says it is often only of medicolegal interest With extensive casualty experience it is extremely irksome to have to X-ray these injuries, knowing perfectly well that there is no fracture, purely for fear of hearing that dread question in court " Tell us, doctor, did you X-ray the ankle?" To the lay mind, and to many doctors, an X-ray is a sine qua non of fracture diagnosis and it almost assumes therapeutic importance Fractures *can* be diagnosed clinically, and in the case of ankle injuries diagnosis rests mainly on the *site* of tenderness—i e, whether over bone or ligament It must be stressed that in only about 40% is this sign clinically useful, because where there is bruising or swelling sufficient to obscure bony landmarks X-ray is mandatory

Dr Garfield did not discuss treatment, but I should like to expound on a principle which is basic to treatment of a sprained ankle—that the attachments of the ligament must be approximated to allow healing of the torn fibres *in the position of minimum length* The conventional application of strapping is therefore useless, except as a compressing agent, and this can be better done with crepe bandage

I have devised a system of strapping which maintains the ligament in its shortest position and, in fact, acts as an artificial external ligament The steps are as follows

(1) The patient is instructed to hold the knee bent and the foot in maximum dorsiflexion and eversion during the procedure (as the anterior talofibular ligament is most commonly sprained)

(2) A U-shaped piece of ' Elastoplast ' about 15 in long is applied from the medial malleolus under the instep, and up the leg to adhere in midcalf region This must be applied under tension, and slightly in front of the axis of the leg (as viewed from the side)

(3) The upper end is fixed with an encircling piece

(4) The ankle-joint is similarly encircled This fixes the lower end of the elastoplast and takes up any slack in the " external ligament '

(5) The foot and ankle are enclosed in orthodox figure-of-8 elastoplast in such a way as to maintain the above position—i e, from the lateral edge of the foot towards the medial malleolus

If there is considerable swelling it should first be reduced with lotions, elevation, and non-weightbearing exercises

The support given should be maintained for three weeks, and the elastoplast may have to be changed during that time

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[2] Selye H. The Chemical Prevention of Cardiac Necroses New York, 1958

[*] Since this letter was written we learn that evidence proving that SC-11927 does in fact block the action of aldosterone will appear in the *Proc Soc exp Biol*, *N Y*, in a paper by C M Kagawa and E A Brown

Normally the 2nd heart-sound is single on expiration but separates clearly on inspiration into its two components of aortic and pulmonary valve closure Narrow splitting indicates that this normal separation on inspiration is reduced in degree, and on quiet breathing the two components of the sound are closer to each other than normal Increased pressure in the pulmonary artery leads to more rapid apposition of the cusps of the pulmonary valve, which causes the sound component of the second heart-sound to occur earlier Narrow splitting is thus a useful sign of pulmonary hypertension, and is often accompanied by increase in intensity of the pulmonary component

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Kuala Belait,
State of Brunei,
[illegible] Borneo

KEITH F D SWEETMAN

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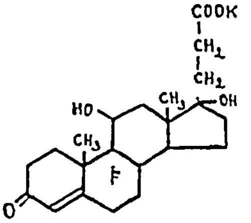

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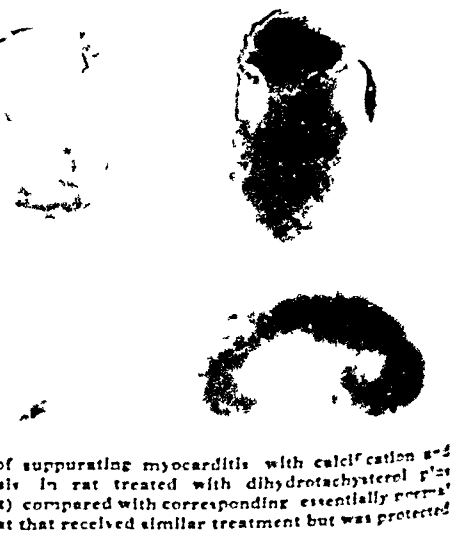

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(2) The fatal cardiotoxic and nephrotoxic actions of dihydrotachysterol plus Na_2HPO_4 may depend upon the "conditioning" action of endogenous mineralocorticoids; if so, blockade of the latter would abolish the toxicity of the treatment administered.

SC-11927 exhibits no detectable inherent toxicity per se when administered at ten times the prophylactic dose level, and even sudden intravenous injection of 2·5 mg. of this compound produces no demonstrable damage. Hence, further studies concerning the possible prophylactic actions of this anti-mineralocorticoid against lesions not primarily due to mineralocorticoid intoxication seems to hold promise.*

This work was supported by grant No. H-3688 (C3) from the National Heart Institute, U.S. Public Health Service, and by a grant from the Gustavus and Louise Pfeiffer Research Foundation.

Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, Montreal

H. SELYE
S. GRASSO
N. PADMANABHAN

RETIREMENT OF MEDICAL RESEARCH-WORKERS

SIR,—Nowadays medical research-workers usually retire at the age of 65. With a life of scientific discipline behind them, many could do useful work for some further years. A few are snapped up by pharmaceutical firms with which they have had previous contact, a few go to W.H.O. or to staff embryo Commonwealth medical schools or are allowed a corner in a University laboratory; a group of elite who would otherwise have retired are producing first-class research in an institute near Cambridge. These facts indicate sustained competence. A large number, from inclination or for health reasons, probably wish genuinely to disengage. A significant number, however, would like to work but are too diffident to mention this audibly: influenced by old-age inferiority feelings, obsessed by forgetfulness of colleagues' names, and recalling their own impatience with clingers to office, they announce their joy in the prospect of time for gardening.

On the hypothesis that a limited amount of facilities suitable for such people already exists or can easily be created—off the career ladders and therefore noncompetitive—I suggest a special employment agency for retired medical (perhaps also other) research-workers. Applicants for full-time or part-time work would register. It is important that not only the previous line of work be given, but also any private bents which in a scientifically trained person, might attract a potential employer (I can call to mind an eminent organic chemist who was expert on insect ecology, a bacteriologist clever at scientific advertisement copy-writing, and so on).

The agency should be non-profit-making and academically sponsored. And this leads to a special point in favour of my suggestion. An initial and annual relevant medical examination should be a condition of acceptance of employment through the agency. While primarily intended to avoid awkwardness, this provision would make available an opportunity for gerontological research on the performance of selected intellectuals. Perhaps the N d Foundation would be interested?

For obvious reasons I sign myself merely

"AGED 60"

IS RADIOLOGICAL EXAMINATION OF THE TWISTED ANKLE NECESSARY?

SIR,—I commend Dr. Garfield's iconoclasm (Nov. 26) in examining the desirability of X-raying every injured ankle.

He is right when he says it is often only of medicolegal interest. With extensive casualty experience it is extremely irksome to have to X-ray these injuries, knowing perfectly well that there is no fracture, purely for fear of hearing that dread question in court: "Tell us, doctor, did you X-ray the ankle?" To the lay mind, and to many doctors, an X-ray is a sine qua non of fracture diagnosis and it almost assumes therapeutic importance. Fractures *can* be diagnosed clinically, and in the case of ankle injuries diagnosis rests mainly on the *site* of tenderness—i.e., whether over bone or ligament. It must be stressed that in only about 40% is this sign clinically useful, because where there is bruising or swelling sufficient to obscure bony landmarks X-ray is mandatory.

Dr. Garfield did not discuss treatment, but I should like to expound on a principle which is basic to treatment of a sprained ankle—that the attachments of the ligament must be approximated to allow healing of the torn fibres *in the position of minimum length*. The conventional application of strapping is therefore useless, except as a compressing agent, and this can be better done with crepe bandage.

I have devised a system of strapping which maintains the ligament in its shortest position and, in fact, acts as an artificial external ligament. The steps are as follows:

(1) The patient is instructed to hold the knee bent and the foot in maximum dorsiflexion and eversion during the procedure (as the anterior talofibular ligament is most commonly sprained).

(2) A U-shaped piece of 'Elastoplast' about 15 in. long is applied from the medial malleolus under the instep and up the leg to adhere in midcalf region. This must be applied under tension, and slightly in front of the axis of the leg (as viewed from the side).

(3) The upper end is fixed with an encircling piece.

(4) The ankle-joint is similarly encircled. This fixes the lower end of the elastoplast and takes up any slack in the "external ligament".

(5) The foot and ankle are enclosed in orthodox figure-of-8 elastoplast in such a way as to maintain the above position—i.e., from the lateral edge of the foot towards the medial malleolus.

If there is considerable swelling it should first be reduced with lotions, elevation, and non-weightbearing exercises.

The support given should be maintained for three weeks, and the elastoplast may have to be changed during that time.

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[2] Selye, H. The Chemical Prevention of Cardiac Necroses. New York, 1958.

* Since this letter was written we learn that evidence proving that SC-11927 does in fact block the action of aldosterone will appear in the *Proc. Soc. exp. Biol., N.Y.*, in a paper by C. M. Kagawa and E. A. Brown.

A sprained ankle should never be underestimated, as it may leave a considerable morbidity of recurrent pain and instability, and I consider that a strict regime, such as the above, is justified

Leicester General Hospital I G SCHRAIBMAN

POST-HERPETIC NEURALGIA

SIR,—I should like to report favourably on the use of ethyl-chloride spraying to treat this condition, as described by Dr Taverner (Sept 24) We have now treated three patients and each one has improved

Male aged 77 Pain behind left ear and down left arm to radial border of forearm A few scars of vesicles visible in distribution of C5 Duration 16 months He began to improve after 4 days spraying and was almost free from pain after 8 days He has had no treatment now for 6 weeks, and is very satisfied

Male aged 79 Pain around left ribs anteriorly Two areas of scarring in distribution of T9 Duration 3 months He began to improve after 3 days, and expressed himself cured after a week No relapse when seen 2 weeks later

Female aged 87 Pain around the left ribs anteriorly and posteriorly Widespread band of scarring in the distribution of T7 Duration 7 months After a week's spraying the acute paroxysms of pain ceased, but further progress was very slow Now, after daily spraying for 4 weeks, she reports a 50% improvement Unlikely to make a full recovery

Before spraying, these patients had been adequately treated with the usual range of analgesics without relief The treatment is not expensive, for one bottle usually suffices for two daily treatments at a cost to the hospital pharmacy of under 2*s*

No advantage was found in using the proprietary product, 'Freon', in place of ethyl chloride

Barnet General Hospital,
Barnet JOHN BARRETT

DYSPNŒA DUE TO SUBCLINICAL AMŒBIASIS

SIR,—Disease of the lung or pleura due to infection with *Entamœba histolytica* is not uncommon

El-Mofti and Moussa,[1] in a study of 900 cases of amœbiasis in Egypt, reported pleuro-pulmonary reactions in 38 cough and chest pain were the chief symptoms and in 15 a pleural effusion developed, while in 6 others a dry pleurisy was present In 7 patients a lung lesion developed when a liver abscess ruptured through the diaphragm

Abdel-Halim and Higazi described 28 cases of amœbiasis with lung changes in which the chief symptoms were pain, hæmoptysis, and cough, although 3 presented with dyspnœa due to a large pleural effusion In most of these cases some lesion was visible radiologically

Carr[3] reported 12 cases with allergic symptoms in a series of 120 cases of amœbiasis, 3 of which presented with asthma In each of these 3 cases permanent improvement in symptoms followed treatment of the amœbic infection, whereas only temporary benefit had been derived from antispasmodic drugs

The case described below seems to be similar to these three cases

A 23-year-old man working in radio assembly, moved to Harlow in September, 1958, and was first seen in January, 1959, complaining of tightness of the chest, associated with attacks of breathlessness and wheezing for the previous three months The attacks came on at any time of day, lasted as long as an hour, and were not relieved by the usual antispasmodic drugs The patient described the attacks as causing him to feel as if he were enclosed in a small space with insufficient air, and stated that his breathing was not noisy as was that of his friends who suffered from asthma There was no previous history of chest or other illness except that during his National Service in Egypt in 1954–55 he had had a mild attack of dysentery, which did not necessitate hospital treatment

His general condition was good, and no abnormal physical signs were found in the lungs or elsewhere Blood-pressure was 132/70 mm Hg Chest X-ray, blood-count, and erythrocyte sedimentation-rate were all normal, multiple-puncture tuberculin test was positive (grade 4), and skin tests, using Bencard reagents, yielded no positive results In view of the previous history of dysentery, the stools were examined for cysts of *E histolytica*, and large numbers were present The patient was admitted to the Hospital for Tropical Diseases under the care of Sir George McRobert, where he received a ten day course of emetine bismuth iodide and this was followed by three weeks of diodoquin at home A big improvement in his general condition followed, and the respiratory symptoms rapidly eased Two months later he was symptom free and this improvement has been maintained for twelve months

It is of interest that when the patient's medical card became available it was found that, four weeks after his return to England in 1955, he had consulted his doctor on account of pain in the chest, which recurred during the next three years, and for which his chest had been X-rayed, although no abnormality was ever reported During the last two years he had complained of breathlessness on several occasions and had had several minor respiratory illnesses described as "flu" On no occasion had his symptoms been sufficiently severe to keep him from work

This case seemed worth recording as an example of respiratory symptoms due to a latent amœbiasis in a young man after National Service in Egypt Similar symptoms in a person of the same sex and age, who has served in the Middle East, may have a similar ætiology

We are grateful to Dr N A F Young for the examination of the stools, and to Sir George McRobert for permission to publish this account

Harlow IAN HAMILTON
URSULA LUTWYCHE

ANGOR ANIMI AFTER BENETHAMINE PENICILLIN

SIR,—In view of your annotation about the effects of aqueous procaine penicillin,[1] we should like to describe the following case

A woman, aged 29, who had had bilateral pulmonary tuberculosis for 5 years, underwent a first-stage thoracoplasty operation on the right, on Aug 4, 1960, under local anæsthesia with lignocaine The postoperative period was smooth, except for fever ranging to 101 F from the 3rd day, and slight tachycardia As well as daily *p*-aminosalicylic acid, isoniazid, and streptomycin, she was also given, on alternate days, injections of 'Benapen Forte', a single-dose vial containing benethamine penicillin 500,000 units, and benzylpenicillin 500,000 units, with buffering and suspending agents

On Aug 12—i e, the 9th day after operation—the patient walked about 30 yards from the ward to the operating theatre where the sutures were removed with the patient seated 10 minutes later, when lying down, she was given her fifth intramuscular injection of benapen forte, 1 vial, into the buttock The nurse and the procedure were the same as for the previous injections The piston of the syringe was withdrawn as usual, before injecting, and no blood was sucked in The injection was not painful, but 2 minutes afterwards the patient tried to sit up and complained of feeling giddy She was helped to lie down, and she shrieked three or four times, and then moaned 'I am gone—I am dying—I am not my normal self' When seen by two of us (T K and R P) within a few seconds, no physical abnormality was found; she was fully conscious and answered questions with slight delay, but she looked dazed, frightened and confused

10 minutes later, when seen by P N K, she still said that she was going to die, that her husband (100 miles away) should be informed by telegraph about her condition, that her own self had departed from her, that something was [illegible]

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1 El-Mofti, A., Moussa, A. H. [illegible] 1951 [illegible]

2 Abdel-Halim, M., Higazi, A. M. *Dis. Chest*, 195[illegible] 34, [illegible]

3 Carr, I. L. *Practitioner*, 19[illegible] 35, 11[illegible]

1 *Lancet*, 19[illegible] 134

changed in her, &c She was very frightened but, apart from tachycardia and a slight rise of blood-pressure, there were no abnormal signs Though her condition did not warrant it, she was given adrenaline 1/1000, 0 5 ml, subcutaneously, followed by promethazine 50 mg intramuscularly, and sips of hot coffee, which she swallowed without difficulty, taking the cup in her hands

As there was no change in her mental state about an hour after the attack, a senior consultant (R K) was called in, he diagnosed "acute psychic shock", and she was given chlorpromazine 25 mg by mouth 30 minutes later she was taken back to the ward, and immediately she expressed great relief and appeared more relaxed. She was stuporose for a few hours, probably from the effect of chlorpromazine, though she was easily woken to take food Later in the evening—i e, about 8 hours after the attack—she expressed regret for her "unusual behaviour" Next morning she had recovered completely

This case has some features which differ from those of Batchelor et al [2] and of Bjornberg and Selstram [3]

1 The reaction occurred after benethamine penicillin and benzylpenicillin, and not after procaine penicillin

2 The patient had not taken her usual breakfast on the morning of the incident, and it was the 3rd day of her menstrual period.

3 Chlorpromazine and/or return to the ward restored her mental equilibrium almost to normal

In March, 1960, another patient—a man of 45—after the first injection of benapen forte, cried out complaining of intense precordial oppression, a feeling of impending death, severe fright, and intense dyspnœa, but these passed off in a few minutes without any special treatment As the "reactions" were very alarming no further injection of benapen forte was given to either of these patients

R PARTHASARATHI
T KARUNAKARAN
P N KRISHNAN
R KALAMEGHAM.

Rajaji Sanatorium
Tiruchirappalli,
Southern India.

TREATMENT OF DRY MOUTH

SIR,—One of the most unpleasant and irritating symptoms of chronic disease must surely be the dry mouth of Sjogren's syndrome and related disorders We have recently had a patient with scleroderma whose chief discomforts were perpetual dryness of the mouth and great difficulty in masticating food the result of atrophy of the mucus-secreting cells of the oral mucosa, and probably also of the salivary glands The physiological stimuli of secretion, such as pilocarpine, were, as might be expected, quite ineffective in stimulating functionally incompetent cells, and continuous sweet sucking left only a nauseous stickiness which was even more unpleasant than the original complaint It seemed logical to give something which had little taste and, being demulcent would leave a thin film of mucus-like material in the mouth for a number of hours and which might stimulate to the maximum any remaining active secreting cells

With these properties in view pastilles were prepared to the following formula

Gelatine	20·0
Glycerine	40·0
Sucrose	5·0
Lemon essence (Ransom 150)	0·6
Sodium benzoate	0·2
Citric acid	2·0
Amaranth solution	1·0
Water to	100·0

This is a modified glyco-gelatine, B.P.C 1949 The mass is poured in dry starch moulds and the pastilles dried for twelve hours in warm air

These pastilles were so successful that it was finally only necessary for the patient to suck one every four hours to ensure a reasonably comfortable mouth and greatly increased enjoyment of her food. She was later discharged with a box of these sweets and writes very appreciatively of their benefit

They may not have as wide a use as the Brompton lozenge and mixture, but we feel they add strength to the same soothing rather than curative range of treatment

PETER DYKES
PETER HARRIS
ARTHUR MARSTON

Queen Elizabeth Hospital,
Edgbaston Birmingham

MEDICINE IN THE FACTORY

SIR,—I was interested by your reference (Dec 10, p 1288) to the fact that appointed factory doctors (A.F D) may be regarded as the principal regular medical force of the factory department This is true, numerically, but the intention and execution of their statutory duties in respect of young people—which form the major part of their work—is on such a limited and superficial basis that many people have recommended that the examinations should be abolished

Potentially, if properly used and organised, the A F D service represents a unique opportunity to provide a general industrial service, and a health service for young people at work, comparable to any enjoyed by the more fortunate section who remain at school or go to universities The Gower report recommended that medical examination should be extended to all young people irrespective of occupation

Unfortunately, the policy of the Ministry appears to be to fragment the health supervision of young people as much as possible Their policy is also apparently to encourage individuals performing statutory duties to make themselves persona grata to the factory occupier and thus be invited to become the paid adviser to the factory Surely, an undesirable division of loyalties

Most A.F D s are busy general practitioners and the pressure of work in practice today is already a frequent source of complaint. There is no doubt that many of them would find it difficult to give more time to the examination of young workers unless the present system was reorganised.

You refer to the fact that 97 7% of all factories employ less than 251 workers The larger factories on the whole have the first choice of young workers, and it is those in the smaller factories who often need, and do not get medical supervision.

According to the annual reports of the Chief Inspector of Factories the number of examinations on first employment is appreciably greater than that for all subsequent examinations including annual re-examination The latter figure should be approximately twice as much as for first examinations

It is the good well-organised firms who report young people for examination and it is those in the less well-organised firms and those who change jobs most frequently who most need the type of supervision which A.F D s could give if they had the necessary time and training The A F D s should go into and know more about small factories than almost anyone else In the course of performing their statutory duties they can also advise on many other problems

For many years now I have been hoping there might be another experiment of the type I have tried here and advocated in my report to which you refer In this connection I am perhaps justified in referring to the opinions expressed by Professor James Mackintosh and King George s Jubilee Trust in the foreword The latter thought that this type of experiment might form the basis for national development. That was five years ago and they may of course be wrong

The pioneer working people realised early in the industrial revolution that to pay special attention to the welfare of young workers was to spearhead improvements for all This may still be true We need today a comprehensive approach to medicine Mind and matter are

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2 Batchelor R C L Horne, G O Rogerson H L Lancet 1951 ii 195
3 Bjornberg A Selstam J Acta psychiat scand 1960 35 129

indivisible, and there is a growing need to pay more attention to the study and avoidance of mental ill-health which contributed so largely to the 300 million days lost from work through sickness every year A good place to start might be to pay more attention to the health of young people at work There is a great need to coordinate as suggested by the Albemarle and Crowther reports and the Dale Committee Why not experiment?

Farnham Royal
Bucks
M E M HERFORD

ASTHMA AND THE SEASONS

SIR,—I saw it suggested [1] that because fungus spores and pollens in the atmosphere were a danger to sufferers from hay-fever and asthma, susceptible patients should shut themselves away in midsummer with the doors and windows closed

A recent survey by Dr H Gough-Thomas of children attending the local-authority asthma clinic in Ealing showed that asthmatic children were most often absent from school during December and January when the air contained 2 5–4 0 *mg of* SO_3 per day, and only small concentrations of spores and pollens In May and June when there was 1 75–1 65 *mg* of SO_3 per day, but high concentrations of fungus spores and pollens, school attendance was very similar to that in control children It seems that sufferers from asthma might have to shut themselves away in midwinter too!

Our impression is that there are many causes of asthma and that each case should be treated on its merits

Hampton Court
MARGARET MCDONALD

THE CASE FOR ABANDONING THE TRENDELENBURG POSITION

SIR,—We think Swain [2] has done a service in writing his paper and giving it as his opinion that the traditional "head-low" position could today be obsolete, with the continuous advance in new drugs and new techniques After all Trendelenberg propounded his views seventy years ago

Your annotation of Nov 26 finished with the pertinent remark that it remains to be seen whether Swain's suggestion finds favour with gynæcologists, most of whom have been trained to operate with patients in the Trendelenburg position

McIntyre,[3] in his paper on anæsthesia for hysterectomy, stated that Trendelenburg stressed the fact that forceful respirations hinder the surgeon by causing the intestines to obscure the operative field Altschule [4] and Case and Stiles [5] have shown that the greater the degree of head-down tilt the more it tends to defeat one of its objects By favouring the development of anoxia and hypercarbia increased respiratory efforts are caused The tilt causes œdema of the head and neck, congestion of the cervical veins, and chemosis

Since 1949, by mutual consent of the three signatories to this letter, Trendelenburg's position has not been used in our group of hospitals As previously reported by one of us (R E L)[6] all abdominal operations performed by another of us (N K) have been performed with the patient horizontal Over 1300 operations have been carried out Respiratory or unforeseen cardiovascular complications in the immediate postoperative phase have been exceedingly rare In spite of routine transfusion with the arm out at just less than 90 there have been no cases of brachial-plexus injury The patient's heels are always elevated on a cushion (rubber or sand-bag) to prevent pressure on the calves and the incidence of deep vein thrombosis has been negligible Pulmonary embolism has occurred twice with one death (eighth postoperative day)

Relaxation has been obtained by *d*-tubocurarine chloride

We do not consider the use of the Trendelenburg position is in the best interests of patients, nor is it necessary for gynæcological surgery We suggest that all gynæcological surgeons who have been reared in the use of the head-low position should try operating with the table flat

NORMAN KIMBELL
R E LODER
Peterborough H S RICHARDSON

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[1] Times, Sep 1[illegible] 1960
[2] Swain J [illegible] Med J [illegible] 1960 ii 536
[3] McIntyre J W R [illegible] 1955 10 359
[4] A[illegible] [illegible] D [illegible] 1943 4 3 5
[5] Case E H Stiles J A [illegible] 29
[6] Loder R E [illegible] 1956 11 [illegible]

Parliament

Human Tissue Bill

ON Dec 8 Mr ENOCH POWELL, the Minister of Health, introduced this Bill into the Commons It extends to Scotland but not to Northern Ireland Its principal purpose is to make clear that parts of a body may lawfully be removed and used for therapeutic purposes, medical education, or research where the deceased had expressed a wish, either in writing or orally in the presence of two witnesses, that his body should be used after death in this way, or where there is no reason to believe that he had expressed any objection or that any relative is opposed to it The Bill provides that the removal may only be made by *a fully registered medical practitioner* and that the coroner's consent must be obtained where there is reason to believe that there may be an inquest In Scotland no authorisation *for removal is to be given if the procurator fiscal has* objected

The Bill also confirms that, notwithstanding the provisions of the Anatomy Act, 1832, a postmortem examination to establish or confirm the causes of death, or to investigate the existence or nature of abnormal conditions may lawfully be carried out provided that there are no known objections on the part of the deceased or of his spouse or any surviving relative

The Bill repeals the Corneal Grafting Act, the provisions of which are included in the more general ones now proposed

Medicine and the Law

Doctors on Council Housing-estates

WHAT appears to have been an unusually determined attempt by a local authority to control the general-practitioner service on a housing-estate has finally come to nothing, thanks to a decision by the Minister of Housing and Local Government

It appears that the Hull Corporation had intended to establish doctors in blocks of surgeries on a new housing estate [1] When the Minister rejected the plan, Dr Gareth King had an agreement with the Corporation that he could build a surgery on corporation-owned land at his own expense Later, however, the Corporation said they were under no obligation to honour the agreement, so Dr King bought a piece of land near his own home and applied for planning permission to build a surgery on it

Planning permission was refused, and the Corporation resolved to acquire the land by compulsory purchase Dr King appealed to the Minister who, after holding a public *inquiry*, allowed Dr King's appeal against the refusal of planning permission and refused to confirm the compulsory purchase order

Dr King observed that "the result of the inquiry is a defeat for those local authorities who want to dictate how the Health Service should be run It defeats any plan to have the medical profession directly under the control of the local authority"

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[1] *Times*, Dec 2 19[illegible]

Obituary

DAVID CARMICHAEL MONRO

C.B., C.B.E., M.B. Edin., F.R.C.S.E.

Major-General D. C. Monro, who died on Dec. 6 at the age of 74, was consulting surgeon to the Middle East Forces during the late war He was largely responsible for reorganising the medical services to fit the new mobile mechanised war of the desert, and it was thanks to his initiative and resource that the forward operating centres of the 1914–18 war were transformed into the field surgical units of the '40s

He was born in New Zealand and went to school at Wellington College but he came to this country to study medicine at the University of Edinburgh where three of his forebears had held the chair of anatomy The family also had a tradition of military medicine—Donald Monro, F.R.C.P. F.R.S., a great-great grand uncle, was senior physician to the Forces and had served in the Seven Years' War—and David Monro soon after graduating M.B. in 1911 joined the R.A.M.C. He served in France and Belgium during the 1914–18 war, and afterwards he took a Regular commission and served as a specialist in surgery in India and Malta. In 1938 he was appointed assistant professor of military surgery at the Royal Army Medical College and two years later he became professor During the late war he was consultant surgeon to the Middle East Forces In 1943 he was a member of the Allied Surgical Mission to Moscow He retired with the rank of major-general in 1945 but was re-employed as consultant surgeon M.E.L.F. until 1948

He was appointed C.B.E. in 1942 and C.B. in 1946 He was also a commander of the United States Legion of Merit and was awarded the King Haakon VII Liberty Cross

Of his work in the Middle East G. A. H. B. writes

"In every way Jock Monro was a most exhilarating personality, and had an intimate knowledge of the surgical work and of the personalities of all connected with it He did a great deal towards the promotion of the wonderful cooperation in M.E.F. He was such a jovial and lovable personality that everyone found it a pleasure to work with him The war in the desert involved huge distances between forward troops and casualty-clearing stations and Jock developed the idea of putting surgical units very far in advance of what had previously been thought possible In 1941 he arranged for two such units to be with the field ambulances and thus saved a great deal of time in operating on seriously wounded men who might have died on the lines of evacuation Together with Sir John Boyd he arranged the close association of field surgical units with field transfusion units and thus it was possible to transfuse to wounded men before operating This development of forward surgery has undoubtedly led to the saving of a great many lives, especially in the case of abdominal wounds where every movement before operation added so much to the risk"

J. S. K. B., who first met Major-General Monro in 1923, when they were on the same senior officers' course at Millbank, relates

"I can still see Jock as he was then—slim, erect, bursting with energy and full of joie-de-vivre. He was the friendliest of souls, as much at home with those of exalted rank (whom in those days we regarded as somewhat formidable) as with the orderlies who attended to our needs in the laboratories Wherever he might be, his infectious laugh was never long silent He had an endless and ever-changing fund of stories which he enjoyed as much as his listeners

"As consultant surgeon to the Middle East Forces in Cairo he was in his element. His duties called not only for a high degree of technical knowledge of the special kind of surgery required in the unusual conditions which obtained there, they called also for great administrative ability and for no small measure of tact, as personalities were many and diverse, yet all had within limits to conform to a common plan. It was my privilege to have somewhat similar duties in another subject, and it was very clear to me that Jock's commonsense appreciation of the special needs of desert warfare, and the modifications he introduced and the encouragement which he gave to all, played a major part in the evolution of an enthusiastic surgical service to which the wounded soldier owed a very great debt And wherever he went there was still the same apposite story and hearty laugh which did everyone a world of good

"After retirement from the active list some 15 years ago we continued to meet at regular intervals Inevitably advancing years took their toll on bodily activity but Jock never grumbled His spirit never changed, and he refused to make an invalid of himself When he could no longer play golf—and what a sorrow this must have been—he turned out regularly to Corps matches and took his stance at some convenient spot where he greeted his passing friends with the same gay laugh we have known for so many years, and which we will never forget"

Major-General Monro married Kathleen Noone in 1942 and they have an adopted daughter

Sir HAROLD BOLDERO

T. C. H. writes

"Harold Boldero combined the most sincere kindness and thought for the individual with great wisdom and regard for general principles If it is true that a sense of proportion is the greatest factor that contributes to wisdom Harold Boldero surely showed this to the utmost.

"His long experience and shrewd judgment were flavoured with a wonderful sense of humour, and many owe him a deep debt of gratitude for his advice and help advice for which they felt they could always turn, however busy he might be. He had a gift of making troubles seem light and would often find an approach to a problem which by its directness and apparent simplicity made its solution easy Boldero had a tolerance and understanding which brought him many true friendships amongst his colleagues of all ages, and his humour and patience made him able to enjoy situations which others found galling or fatiguing

"He had little regard for who got the credit provided he could feel that a job was well done—and the thought and skill which he gave to preparing an agenda or a draft made the burden light for others His letters were like himself—clear amusing, always to the point, and in a style that was especially his own.

"He was a man whose interests were wide and varied and his presence at a dinner party would ensure its success His witty and sometimes apparently cynical comments on the foibles of human nature and the oddities of his times gave no indication of his great sympathy with his fellow men perhaps particularly with the young He showed none of that weakness of older men—a too great preoccupation with the past—but was ready and anxious to move forward to new ideas and new methods he had a constructive attitude to suggestions where others might criticise without offering useful alternatives He will be deeply missed not only for the help, but even more for the friendship and pleasure which his life gave to so many"

Appointments

CARR DOROTHY M. M.B. N.U.I., F.F.A.R.C.S. honorary anaesthetist Italian Hospital London.

EARL, C. J. M.D. Lond., M.R.C.P. consultant physician neurological department London Hospital.

FORDYCE F. W. M.B. Durh. school M.O. Northumberland.

HILTON R. W., M.B., B.Sc. Aberd. assistant M.O. and school M.O. Bradford.

MCDONALD E. L. M.D. Cantab M.R.C.P. consultant physician, cardiac department London Hospital.

MCNAIR T. J. M.B. Edin., F.R.C.S. consultant in general surgery, Edinburgh teaching hospitals

MORTIMER DOUGLAS M.B. Aberd. assistant M.O.H. and school M.O., Wakefield.

ROSS J. A., M.B.E. M.D. Edin. F.R.C.S.E. consultant in general surgery, Edinburgh teaching hospitals

Liverpool Regional Hospital Board

GRAY T. D. H. M.B. Lpool F.R.C.S. part-time consultant ophthalmologist Broadgreen Alder Hey Children's and Birkenhead General Hospitals

HONEY, G. E., D.M. Oxon. M.R.C.P. consultant physician Walton Hospital.

JONES, E. S. M.B. PH.D. Lpool M.R.C.P., D.T.M.&H. consultant physician, St. Helens and district H.M.C.

Notes and News

THOMAS LINACRE

THE 500th anniversary of the birth of Thomas Linacre is being celebrated by the Royal College of Physicians of London this year, and on Dec 8 the Linacre oration was given by Sir George Clark, the historian

Although the college was in form a royal foundation, Linacre, he said, has always been rightly regarded as its real founder He was also its president from the beginning in 1518 until his death in 1524, and he was its first benefactor His wealth was acquired at least partly from a successful professional career by the end of which he was the head of the medical household of King Henry VIII Among his contemporaries, however, he was chiefly famous as the first Englishman who made a substantial contribution to the revival of Greek learning and as the first Englishman with a European reputation as a classical scholar These two aspects of his achievement may seem now to have little relation to one another, but in fact they formed a well-knit unity

He was born in 1460 or 1461 (the exact date is unknown) He was *Cantuariensis*, but this may mean that he was born not in the city but in the diocese of Canterbury Modern research has demolished the accounts of his parentage and early years which were formerly accepted, and the first well-attested fact of his life is that he was elected a fellow of All Souls College, Oxford, in 1484 Whether he began to study Greek or medicine in Oxford is unknown, but there were opportunities in both fields One of his colleagues at All Souls, sixteen years his senior, lived to be a charter-fellow of the College of Physicians, and another, his junior, was the first to be admitted after election

In 1487 Linacre went to Italy, and it was not until 1499 that he returned to England to settle down During these years he worked in the inner circles of the revival of learning In Florence, at the court of Lorenzo the Magnificent, he learned Greek from the best masters In Rome he served for a year as warden of the English hospice In Padua he took his degree as doctor of medicine In Venice he lived for several years in the house of Aldus Manutius, the greatest of all printers of classical texts He devoted himself especially to the manuscripts of Greek scientific and medical works When he left Italy he was a recognised authority on these, and he had completed the first of his works to be published, a Latin translation of the little treatise of Proclus on the terrestrial globe

Back in England he was one of the leaders in the wonderful circle—Grocyn, Latimer, Colet, Erasmus, Thomas More, and their friends—who began the continuous history of Greek scholarship and teaching here His friends reproached him with being slow to publish, but, in spite of the other calls on his time his achievement in that line was very considerable He lectured on the scientific work of Aristotle, but his published work dealt mainly with Galen, who was for that time the most important of the Greek medical writers Galen's works were published in Greek in five large *folio* volumes by the successor of Aldus in 1525 but before that there was a period of about thirty years in which the most fruitful method of recovering Galen's medical science was to translate from the manuscripts into Latin Linacre, with a higher standard of scholarship than most of the translators, dealt in this way with two of Galen's major works, and his translations ranked as standard works, often reprinted in various Continental cities Besides several shorter pieces of Galen and a school Latin grammar he provided other scholars with a valuable tool, a full grammar of the Latin language This too was long and widely celebrated

Except for one visit to Paris as physician in the suite of King Henry's sister Mary Queen of France Linacre spent the years of his prosperity at his house the Stone House in Knightrider Street close to St Paul's Cathedral London in his day was exceptional among the greater cities of Europe in having no organised body of physicians This does not mean that its medical doctors were an undisciplined rabble they were very few in number and they were bound together by a great ethical and educational tradition But there was a need for system in the granting of licences to practise and for direction in the repressing of irregular practitioners These were the ends which the College of Physicians furthered It was not intended to be a teaching body for that purpose Linacre conveyed landed estates which he had bought in Kent to trustees who were to establish medical lectureships in Oxford and Cambridge So far as the London college followed any existing models, it seems to have adopted some features of English guilds and companies, and some of Florentine, Venetian, and other Continental medical corporations

Many writers, Sir George said, have represented Linacre as a forerunner of the scientific spirit or even of the Protestant Reformation We know too little of his mind to guess what he thought of the new religious movements which afterwards divided the circle of his friends During his lifetime they were scarcely heard of in England He was an ecclesiastic, he held many Church preferments, and he was ordained priest as late as 1520, when he was about 60 The many-sided Italian renaissance, in which he played more than a minor part, had an element of science in it, but much else too We do not know whether Linacre ever heard of the anatomical investigations of Leonardo da Vinci, but we do know that he was a fellow pupil of Pope Leo X So far as his mind and action are known to us, it seems that he used his learning and his wealth in the ways that the ideals of his early manhood dictated

THE KING'S FUND

THE Duke of GLOUCESTER, presiding at a meeting of the general council of King Edward's Hospital Fund for London on Dec 8, said that the Fund was constantly looking for new ways in which to help patients by improving conditions in hospitals To this end the reports provided by the official visitors were most valuable, and, as examples, he cited the survey on noise control, of which some 14,000 copies had been circulated since 1957, and the recent manual on hospital visiting,[1] for which the demand was so great that a second edition of 5000 had to be ordered within ten days of publication The preparations for courses in work study at the Hospital Administrative Staff College were now complete, and it was hoped gradually to train work-study officers for all the hospital groups which needed them A three-month course for administrators from the Commonwealth was to begin in April

Lord McCORQUODALE, the chairman, said that there had been exceptionally heavy non-recurrent expenditure owing partly to the purchase of a site in Holland Park on which a new and larger staff college for ward sisters was to be built, and the purchase and adaptation of a house which would enable the Hospital Administrative Staff College to take 25 additional students

Two new committees were to be set up—a colleges committee to deal with matters of policy regarding the three staff colleges and school of catering, and a hospital development committee to consider projects submitted to the Fund, such as a centre for information on experiments proceeding throughout the hospital service It seemed likely, in Lord McCorquodale's view, that in the next decade it would become less necessary to make grants for hospitals needs and that more attention would be given to inquiry and experiment, and to the pioneering of new ideas and new schemes for the benefit of hospitals

HALF-WAY HOSTEL

EARLIER this year Dr D H Clark and Mr L W Cooper described the beginnings of an interesting Cambridge experiment in community medicine[2] Winston House, with the triple support of the Cambridgeshire Mental Welfare Association and County Council and the S O S Society, was opened in October, 1958 as a hostel for patients who had lately left a mental hospital and were ready to try once more to earn their own living During its first year, rather surprisingly, [illegible] never completely full, but the report of the second year suggests that this was chiefly because the right people had [illegible] learned of its existence For the whole of the second year it has been nearly full, and indeed in the latter half there has always been a waiting-list The average daily number of residents was 21 There were 57 admissions during the year (compared with 36 in the first year) and 50 departures (22 in the first year)

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[1] See *Lancet*, Dec 10, 1960, p 1311

[2] [illegible] 1960, i, 5[illegible]

The 50 departures were made by 46 people, for sometimes residents return after an unsteady independent start 11 departures were regarded as thoroughly satisfactory, and 15 as fairly satisfactory Of the others, 7 residents returned to a mental hospital Only 4 residents (2 alcoholics, 1 aggressive psychopath, 1 inadequate psychopath) had to be asked to leave because their behaviour was disturbing the hostel Taking the results of the first two years together, 41 people—or about two-thirds of those admitted—have made a satisfactory transition to the outside world

During the year the age-limits for admission have been widened, and residents now range from sixteen-year-olds to those in their sixties As the hostel has become more widely known, more patients have been drawn from other hospitals than Fulbourn Hospital and from more distant parts than Cambridgeshire Last year Dr Clark suggested that admissions of this kind would be welcome, for they would bring new interests to the hostel, and this has proved to be so Mr Cooper, the warden, has also welcomed this year as residents some professional men and women "Graduates, military officers, and public schoolboys have mixed and learned together with labourers, hospital ward maids, domestics, shop and factory workers All have a common meeting ground of recent mental illness and each appreciates the others' need of sympathy, friendship, encouragement, and understanding in a community life" All the residents of Winston House are selected because they are thought to be capable of achieving independence, but a few have failed, and Dr Clark admits that during the year he has become more and more aware of the need for hostels for people who are never likely to be able to live on their own

ANTIBIOTIC OR SULPHONAMIDE?

THE increasing use of sulphonamides as an alternative to antibiotics is discussed by Bergfors[1] in a sort of sulphonamide-antibiotic A B C designed primarily to help the general practitioner Since the early days of the sulphonamides there has been a considerable reduction of side-effects and complications without loss or efficacy thus a complication-rate of 0 4% for one of the newer ones can be contrasted with a complication-rate of 18 6% for one of the older There has also been a change in the spacing of the doses, from one every 4 hours to one or two every 24 Bacterial resistance seems to develop more slowly to sulphonamides than to antibiotics, and many of the bacteria primarily resistant to antibiotics are sensitive to sulphonamides As regards expense, one of Bergfors' tables shows the cost of a 6-day course of treatment under policlinic conditions for a 3-year-old child who has the choice of ten sulphonamides and nine antibiotics The cost of the sulphonamides ranges from 4 20 to 11 95 Swedish crowns, while the cost of the antibiotics ranges from 7 70 to 40 30 But Bergfors notes that in Sweden the sale of one of the cheapest sulphonamides is quite modest, whereas a comparatively expensive one accounts for more than half of all sales for the sulphonamide group

IMPENDING SURVEY OF MENTAL HEALTH SERVICES

ADMINISTRATIVE changes in psychiatry have been considerable, and the Mental Health Act of 1959 will alter the scene even more Systematic reporting and evaluation of these changes have been slow to get under way, and it is excellent news that P E P, with the help of the Nuffield Provincial Hospitals Trust, have started a three-year survey of the mental health services with particular emphasis on community care As a P E P pamphlet[2] points out

> "It is unusual for new legislation to be preceded or accompanied by systematic investigation, as contrasted with the more discursive type of enquiry characteristic of Royal Commissions, which might provide a factual basis for policy-making and planning"

It seems that this survey will cover the structure and operation of services in selected districts together with the social and personal consequences for patients and families, and make a sort of time and motion study of the various staff members involved The role of the family doctor, and attitudes of profession and public towards mental illness, are included, and there will be a glance at the services for the mentally subnormal No controlled experimental approach to assess the effectiveness of new methods seems to be envisaged The P E P pamphlet also summarises historical trends in psychiatric care, gives short accounts of local-authority services (existing and proposed), and describes an interesting follow-up of discharged patients in Scotland P E P expects to collaborate with other researchers, and, if the project is to be carried through at all, will clearly need much cooperation from the many who are involved We hope that this will be given freely

FILMS ON HOSPITAL INFECTION

TWO recent films are concerned with the spread of resistant strains of staphylococci in hospitals and recommend methods of reducing the risk of cross-infection

Hospital Sepsis a Communicable Disease[1] (16 mm, sound, colour, 29 minutes, U S A, 1959) illustrates the case of a patient admitted to the Peter Bent Brigham Hospital, Boston, with a specifically identifiable staphylococcal infection Although she was nursed in a specially prepared room, the organism was later identified throughout the hospital The film examines the concentration of organisms on and around the patient following various nursing procedures and the routes by which the infection left the room Among the reservoirs and multipliers considered are the floor-mops, bed-linen, mattresses, drinking-water, soap, and the ventilation plant, and suggestions are made for dealing with these and with other infected material leaving the room

This excellent film presents the problem vividly and gives sound advice It could usefully be shown to most of those who work in hospitals, including ward orderlies, engineers, and administrators

Hospital Cross-Infection Dressing Techniques in Wards[2] (16 mm, sound, colour, 26 minutes, Great Britain, 1960), which was made with the cooperation of the Sterilising Research Unit at Little Bromwich General Hospital, Birmingham, discusses the spread of organisms from an infected patient or member of the ward staff to the reservoir and the target, and shows how weaknesses in normal hospital routine and procedures may promote this spread A separate room on a ward, built on the principle of an operating-theatre, in which all dressings are carried out is suggested, and the advantages of a central sterile supply department and of the use of disposable materials are mentioned Finally wound-dressing techniques, first for use by a single nurse and then by two nurses, are demonstrated

Although a good film, this is not as well organised as the American one, but the recommended nursing procedures make it valuable for use by sister-tutors

University of Dublin

On Dec 8 the following degrees were conferred

M D—F L Willington

M B, B Ch, B A O—A D S K Allen E F Brown Judith A Bryan, D D Duncan A N Dunn J G G Eglinton Celia F Twisleton-Wykeham Fiennes J J Gorman, J D McCarter Sheila P McGuinness, Bohdan M Meeson Denise R Millin R A H Mooney J R Press P J W M Sang R E Snow, Margot V Thomas, Deirdre M Verling

L M, L Ch L A O—Archibald Redman

British Association of Otolaryngologists

The following officers have been elected

President, Prof V F Lambert, immediate past president, Mr C Gill Carey, vice-president, Mr M L Formby, hon treasurer, Mr J C Hogg, hon secretary, Mr G H Bateman

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[1] Bergfors P G *Svenska Lakartidn* Oct 14 1960

[2] Community Mental Health Services *Planning* 1960 26, no 447 Published by Political and Economic Planning 16, Queen Anne s Gate, London S W 1 Pp 15 2*s* 6*d*

[1] Hospital Sepsis a Communicable Disease (film and booklet) available without charge from Johnson & Johnson Ltd, 260, Bath Road Slough, Bucks

[2] Hospital Cross-Infection Dressing Techniques in Wards (film and booklet) available without charge from Smith & Nephew-Southalls Ltd, 5/7 Singer Street, London E C 2

Royal College of Surgeons of England

At a meeting of the council on Dec 8, with Sir Arthur Porritt, the president, in the chair, Lord Kindersley was admitted to the court of patrons Prof Digby Chamberlain was appointed Bradshaw lecturer for 1961, and Mr G T Hankey was awarded the John Tomes prize for 1957–59

Diplomas of fellowship were granted to the following

C M Ruben A E Steel J H F Batstone, S K Bosher, D C Gardner, R A James H J S Waldeck J G Jeffreys W M Mee E F Denman G C W Baker B G Andrews G R I Roberts Molly E Wakely A W F Lettin Theodore Chukwuemeka Ezeokpue Mbanefo Ajeet Bans Lall Gulati Christopher Wastell Alexander Cort, G N McG Orr, Samuel Gopal Ramaiya A J de Bruin P D Livingstone Birinchi Prasad Samanta Hyman Kramer D J Adams Arthur Bates I F Maclaren R K McRae, Harish Chandra Puri, Dhun Dinshaw Sumariwalla P J Chesterman Ahmed Abdulla Kazim J P Masterton C R Fenton B G Haggart D W M Haw, Hon Fih Ho, J G Mander, Thamotherampillai Nadarajah Shanmugalingam Trevor Sussman, J W P Bradley G G Dinning, Earl Mink Teh Lu G W Crock D L Crosby, D D Foster, R W Goonewardene A H Grabham, J M S Hague M B Heywood Waddington, C T Howe J A Hunt F O G Kirwan Adi Eruch Mody, A E J Mullins, Sannapareddi Sreenivasulu Reddy C J C Renton I G Schraibman, Letchumanan Sivaraman, M J Betty, G J Bougher L J Caust B C Cohney, G A G Decker, K M Dickinson J R P Gibbons, D U Hay, D W Hossack, J B Laine D J McAuliffe R A Owen Ballambetto Yogish Pai Henry Poirier, D M Ritchie G R Thoms D L Annetts, Baldev Raj Bahl, P M Binns F J Collins, S R Duke Hassanein Mohamed Hassanein El Sherif W M P Fennell, D C Glenn M C Green W G Harris P McR Higgins, C N Hudson J N Kille Richard Lenaghan C J H Logan Gearoid Lynch Brian McKibbin, Prithvinath Dinanath Madhok, H R Magee P M Meffan, G J Ormandy W H Reid, R L Rothwell Jackson C F Rowell, Leo Rosner P M Scott Bhanu Ratilal Shah H L McI Smith A P Wyatt Hameed Ud Deen Ahmed, C W P Canagaretna Jagdish Kumar Chaudhry, Eugene Poh Hwye Chu, Sohan Lal Johari, K I King, Franklin Wang Pong Li W S Pease, N M A Rogers, J A Russell, R T Southwood, Jamsheed Cooverji Taraporvala, Marthanda Varma Sankaran Valiathan P J Venter, Ivo Smith, M I Strang, Vasant Charuchandra Talwalker

Royal Faculty of Physicians and Surgeons

At a meeting of the faculty on Dec 5, with Dr J H Wright, the president, in the chair, the following were admitted to the fellowship *qua* physician

John Ballantine Shantakumar Dnyaneshwar Bhandarkar Hugh Conway, Bruce Cruickshank, Jayanta Kumar Dutta A T Elder Arvind Sadashiv Godbole Mohammed Shamsul Haque Cheng Hing Ip, Tit Shing Ip, A I Macdougall, Kantibhai Maganbhai Patel

Royal College of Physicians of Edinburgh

The following officers have been elected for the coming year

President, Dr J D S Cameron, vice president, Dr I G W Hill, members of council, Dr J G M Hamilton, Dr Thomas Anderson, Dr A W Wright, Dr H J S Matthew, Dr C W Clayson, treasurer, Dr J A Bruce, secretary, Dr R F Robertson, hon librarian, Dr W A Alexander, registrar, Dr William Macleod

Welsh National School of Medicine

Dr J G Leopold has been appointed senior lecturer in pathology

Hunterian Society

The dinner meeting of this society on Monday, Dec 19, at the Talbot Restaurant, London Wall, London, E C 2, will be followed at 8 30 P M by a discussion on the Mechanism of Conversion to Brainwashing, which will be opened by Dr W W Sargant

European Academy of Allergy

A meeting of this academy will be held on April 28 and 29 in Berlin The main subjects chosen for discussion are differential diagnosis of bronchial asthma and destructive emphysema of the lung and neurodermatitis and contact eczema The speakers will include Prof Jethro Gough Further particulars may be had from Dr H Michel, Berlin-Charlottenburg 9, Krankenanstalten Westend

Sully Hospital

On Monday, Dec 19, Sir Clement Price Thomas the president of the Welsh National School of Medicine, is opening the new cardiac laboratory in this hospital

This department has been equipped by the Welsh Regional Hospital Board with Philips cineradiography apparatus including an 11 in and 5 in image intensifier A Philips closed-circuit television [illegible] cardiac catheterisation with the 5 in image intensifier Other equipment in the laboratory includes a Sanborn [illegible] channel direct-writing [illegible] pressure transducers [illegible] D[illegible] and equipment for [illegible] blood-gas analysis and radioisotope measurements

Leeds Neurological Sciences Colloquium

A meeting of the colloquium will be held on Tuesday, Dec 20, at 5 15 P M, at the General Infirmary at Leeds when Sir Russell Brain will speak on the Cerebral Basis of Mind

Army Appointments

Major-General W R M Drew has been appointed commandant and director of studies to the Royal Army Medical College in succession to Major-General W D Hughes Brigadier W H Hargreaves has succeeded Major-General Drew as director of medicine and consulting physician to the Army

Prof T C Gray has been appointed honorary consultant in anæsthetics to the Army, and Dr R Miles Gibson honorary consultant in neurosurgery to Catterick Military Hospital

Medical Women's Federation

Christine Murrell fellowship (£150) —The Federation invites applications for this award from women doctors Full details will be found in our advertisement columns

Tumour Biology

A meeting on this subject, organised by the Cancer Research Commission of the International Union against Cancer, is to be held in Warsaw, Poland, from May 22 to 27 Further particulars may be had from Prof O Muhlbock, chairman of the Cancer Research Commission, Sarphatistraat 108, Amsterdam, Holland

Hostel for Deaf Children

King Edward's Hospital Fund for London has made a grant of £20,000 to buy and adapt 6, Castlebar Hill, Ealing for use as a hostel for deaf children who are attending the audiology unit of the Royal National Throat, Nose, and Ear Hospital

The new hostel (which adjoins the existing hostel for mothers and very young deaf children) will take 20 children of varying ages and will enable longer and more intensive periods of training to be given Mothers, and occasionally fathers, will be able to stay at the hostel from time to time

Opportunities in Hospital Administration

Applications for training posts for prospective hospital administrators are invited by the Minister of Health and the Secretary of State for Scotland under the National Recruitment and Training Scheme begun in 1956

The posts are open both to young officers in the National Health Service and to university graduates and professionally qualified people who wish to make hospital administration their career They are tenable for three years beginning in October, 1961 The normal age limit is 30, but candidates up to the age of 35 may be considered The student administrators will be given practical experience of hospital administration with different hospital authorities, together with courses of instruction at the Hospital Administrative Staff College of King Edward's Hospital Fund for London or at the University of Manchester Their fees will be paid and they will receive a salary beginning at £605 At present 12 candidates are undergoing training, 4 of them women With one exception, the first and second groups of trainees have found permanent employment in the hospital service

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Sir Harry Platt has been appointed the Ministry of Labour's regional medical adviser for the north west

Mr R B Zachary has been elected a corresponding member of the Czechoslovak Medical Society, J E Purkinje

The French review *Agressologie* is offering a prize (2000 NF) to workers under 35 years of age for an essay on a clinical or experimental subject "de physio-biologie ou de pharmacologie appliquées aux effets de l'agression" Particulars may be had from the journal, 14 rue Drouot, Paris IX

CORRIGENDA *New Procedures*—In th[illegible] chemical [illegible] appeared at two points where [illegible] been printed The *Procedures* are published by the [illegible] Clinical Biochemists and the address [illegible] department of clinical pathology, Royal Infirmary [illegible]

P[illegible]—In the article by Dr [illegible] and Dr [illegible] (Dec 3, p 1217) Dr [illegible] should have been shown as [illegible] in Columbia [illegible] The address [illegible] Avenue, New York 21, N Y

The Lancet · Saturday 24 December 1960

A THIRTY-YEAR SURVEY OF ACUTE INTUSSUSCEPTION IN CHILDHOOD

269 CASES

D CAMPBELL COOKE
F R C S E
SENIOR SURGICAL REGISTRAR

E C LEWIS
M B Lond
REGISTRAR

THE ROYAL HOSPITAL, WOLVERHAMPTON, STAFFS

THIS paper is a survey of all cases of intussusception in childhood which have been admitted to a general hospital during the thirty years 1929–58 For the purposes of this series, childhood has been arbitrarily defined as the period from birth to 5 years

Mortality has decreased in the period under review (table I) The apparent rise in the second decade is probably the effect of the first two years of the war, when there was a general disruption of the medical and hospital services Though the improvement since 1929 is gratifying, there are still no grounds for complacency

TABLE I—CASES AND MORTALITY

—	Number of cases	Deaths	Mortality %
1929–38	91	16	17 6
1939–48	76	20	26 3
1949–58	102	9	8 9
Total	269	45	16 7

It is interesting that, of a total of 22 cases requiring resection, 7 were operated on between 1929 and 1948 with 6 deaths, but, between 1949 and 1958, a further 15 resections were performed with only 4 deaths

The mortality for the whole of this series was 16 7%

Though this disease affects some of the healthiest of our child population, it has seldom been reviewed in Britain In Australia, on the other hand, where great attention has been paid to this condition since the turn of the century, Hipsley (1926) and Vickers (1926) were able to record mortality figures of 5% and 11 5% respectively as long ago as 1926

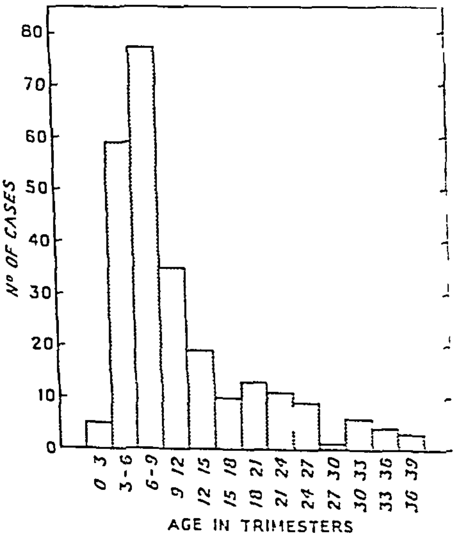

Fig 1—Age-distribution.

We feel that a further survey is due, if only to emphasise the importance of early reference to hospital of any suspicious case Even today many patients are referred to hospital at a distressingly late stage of the disease

This series consists of 269 cases, with 45 deaths

Age

The age of the patients in this survey closely follows that in most other series, the largest group consisting of children between the ages of 3 and 9 months (fig 1) As would be expected, the mortality falls with increasing age, it was 31% at 0–6 months, 14% at 7–12, and 0 7% at 12–24

Sex

There were 176 boys and 83 girls, an approximate ratio of 2/1—as in most other recorded series An exception was the Newcastle series (Morrison and Court 1948), covering the period 1944-46, where 45% of the cases were girls The mortality in our series did not vary between the sexes

Seasonal Incidence

The number of cases seems to vary considerably from year to year, ranging from 4 in 1935 to 15 in 1956 The incidence (fig 2) agrees roughly with that given by Strang (1959), and is greater in the spring and summer

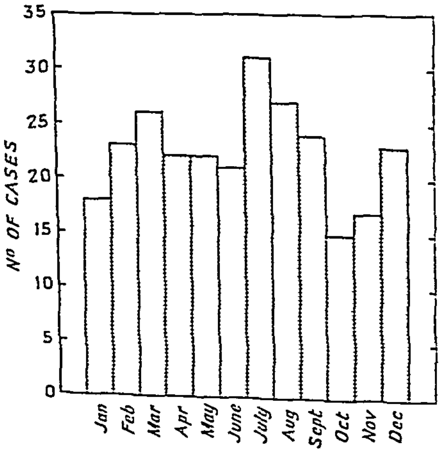

Fig 2—Seasonal distribution

Ætiology of Intussusception

Though in adults 80–90% of the cases have a definite causative lesion, the ætiology of this condition in children remains largely hypothetical

In a few children, a definite lesion is found to be the cause—for example, a Meckel's diverticulum, a polyp, or even intestinal reduplication In this series, the intussusception was due to an inverted Meckel's diverticulum in 4 cases, and in another case an intussusception recurred with the appendix stump forming the apex, appendicectomy having been carried out at the first operation In the remaining 264 cases, a definite cause was lacking

Dietary changes or indiscretions have been incriminated, but these, because of the wide variations in the management of infant feeding, are very difficult to assess The extent to which unofficial supplements are added to the feeds remains unknown, particularly when mothers are working and children are left in the care of relatives or friends In these circumstances, lack of general cleanliness and sterility of feeds may provide a source of infection Mr C Vincent Patrick tells us that he knows of no privately treated cases of intussusception in this area for many years

7165

Nothnagel in 1898, after experiments with rabbits, popularised the hypothesis that intussusception results from intestinal spasm, and he suggested that a contracted area was propelled onwards like a bolus of food. With this hypothesis as a basis, other causes of spasm have been put forward. It has been suggested that the change from milk to a more solid diet may cause intestinal irritability, and thereby spasm. Spasm undoubtedly occurs in gastro-enteritis, and in a few cases a recent history of intestinal upset can be obtained. More recently, a delay in the development of the inhibitory sympathetic system to the small bowel has been blamed, producing spasm in the ileum and relaxation of the ileocæcal valve.

Linked with, and added to, the concept of spasm must be an abnormality of motive power in the shape of exaggerated or perverted peristalsis. Bowel movement may be exaggerated by changes in the volume of bowel content, or by the action of drugs or noxious agents within its content, or via the blood-stream, provided infection is not severe enough to produce paralysis and the dilatation of ileus. Grossly abnormal peristalsis must sometimes take place or else a retrograde intussusception would be an impossibility.

A child of 12 months had a history of being off colour and irritable for seven days, five days diarrhœa (chiefly after meals), and vomiting with screaming attacks for four days. Two days before admission a questionably blood-stained stool was passed, after which there was no bowel action. At operation, she was found to have three separate intussusceptions—an ileocolic, a retrograde colocolic, and an advancing colocolic. These were reduced with ease.

This child illustrates well the beginning of a prodromal gastrointestinal upset, with ensuing derangement of peristalsis leading to intussusception. Recently a child, operated on in another hospital of this group, had no less than 15 separate intussusceptions, which must indicate a most widespread peristaltic upset (Hadfield, personal communication).

It is suggested that infection plays a large part in the production of this exaggerated peristalsis, and possibly in the origin of local spasm by the irritant effect of swollen Peyer's patches and enlarged mesenteric glands. Peyer's patches are difficult to recognise at operation when the bowel is reduced and œdema from strangulation involves the whole region of the apex. In a case coming to necropsy shortly after reduction, definite hyperplasia of lymphoid tissue was seen, with bulging into the lumen of the bowel, and in places a pseudopolypoid appearance. Against this hypothesis of local tumour formation by hyperplasia of Peyer's patches, the experience of surgeons operating on cases of Peutz-Jegher syndrome has been that the polypi responsible for the intussusception have been 1–1½ in. in diameter—large enough to cause obstruction of the bowel. Similarly, other small-bowel tumours causing intussusception do not do so until they are so big that they cause obturation. If Peyer's patches are to cause intussusception, they must have enlarged sufficiently to obstruct the bowel almost completely.

Enlarged mesenteric glands are present in many cases, and they appear to precede the intussusception rather than to follow it. They have often been found in cases operated on four to six hours after onset of the illness.

In this series, pyrexia has been a feature on admission. Some pyrexia would perhaps be expected in any illness producing irritability, screaming, and dehydration, but of the last 63 cases, 35 had a temperature of over 99·5 and in 12 it was over 100·5. This pyrexia is not in accord with most standard descriptions where the temperature is stated to be normal or subnormal, or else is not mentioned at all, but agrees with the findings of Morrison and Court (1948).

An analogy can be drawn between the findings in intussusception and those in nonspecific mesenteric adenitis.

In the latter, an older child, commonly with a history of recent upper-respiratory-tract infection or tonsillitis, is admitted with high temperature and attacks of colicky abdominal pain, sometimes of extreme severity. Between attacks of colic, there is entire freedom from pain and the child may be found sitting up and taking notice, or even playing with toys. Tenderness, the site of which alters with position, can be elicited, and auscultation will often confirm the presence of exaggerated peristaltic sounds. These signs suggest hyperactive bowel, and the tenderness might well indicate an area of local spasm.

At laparotomy, there is discrete enlargement, usually more marked in the ileocæcal region, of the mesenteric glands of the ileum. A varying amount of free serous fluid is present in the abdomen. The ileum may appear normal or may show a mild serous hyperæmia. Occasionally, it may be the seat of palpable œdema of the whole thickness of the bowel wall. The appearances of the lymph-nodes and of the bowel are of inflammation, suggesting a response to infection.

The symptoms and intra-abdominal findings in these two conditions suggest a common causative agent, but it does not explain why intussusception is less common in older children.

Some other factor must be present, and the only other variable appears to be the increased diameter of the bowel in older children. Zachary (1955) suggested that the intussusception would be tighter in a younger child because of the smaller bowel diameter. He was able to reduce more cases by barium enema in infants over 6 months old than he could in those under 6 months, irrespective of length of history. In our series, 64 cases were under 6 months and 9 of these (14%) required resection. Of the remaining 205 cases, 13 (6·3%) required resection. A reasonable assumption is that intussusception is rarer when the bowel lumen is large, because spontaneous reduction probably takes place more readily.

Finally, anatomical factors may play a part. In many cases of ileocolic or ileocæcal type, abnormal mobility of the ascending colon and cæcum is noticed, and this may influence the final outcome. In recent cases, more critically examined at operation, it has appeared that the greater the mobility, the less likelihood there is of compression of the mesentery with consequent strangulation; conversely the more difficult cases to reduce have been those with a relatively fixed cæcum. The prominent and protruding ileocæcal valve of infancy has received its share of the blame, and clearly it might form the apex of an ileocæcal intussusception. In this series, however, the ileocolic type has been much more common than the ileocæcal type.

Apparently no one factor can be held responsible for intussusceptions at all levels of the intestinal tract.

Clinical Features

In assessing the symptoms in this series, we have often found it extremely difficult to pinpoint the onset of intussusception in the midst of a gastrointestinal or respiratory illness. We have tried, however, to take the point at which symptoms became progressive and relentless rather than that marked by intermittent attacks of colic or vomiting which seemed to signal the onset of illness in a proportion of children.

The length of history does not always seem to correpond with the severity of the intussusception, the degree of intestinal obstruction, or the distance the apex advanced

Some cases with short histories and a relentless course have come to resection within twenty-four hours, while in others with long histories and slight constitutional signs, intussusceptions have reduced easily These two groups do not seem to be confined to any particular type

Fig 3 shows the series divided into three groups according to the length of history, where this could be accurately obtained 80 seems a very high figure for cases with a history of more than forty-eight hours, and analysis by years shows that the number of late cases has actually increased over the last few years of the survey This is perhaps surprising, because doctors refer their patients to hospital earlier than in the past In 1929–38, 76% of cases arrived in hospital within twenty-four hours of the onset of the illness, but in 1949–58, the percentage of cases arriving within twenty-four hours had fallen to 57

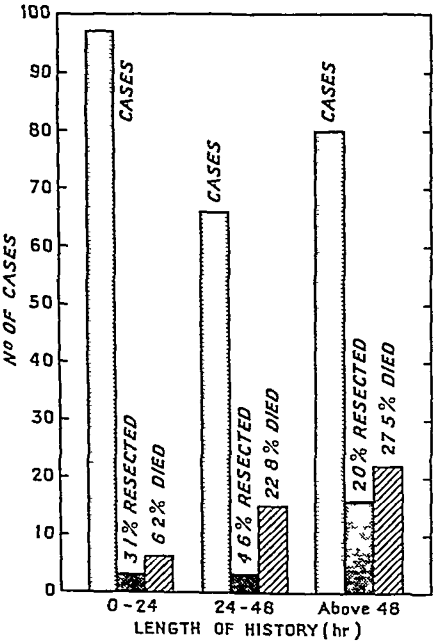

Fig 3—Numbers of cases by length of history with the resection-rates and mortality-rates

The resection-rate increases only slightly with the length of history, but the death-rate rises considerably after the first twenty-four hours After forty-eight hours, there is little further increase

To the recognised tetrad of symptoms—pain, vomiting, rectal bleeding and palpable mass, there is little to add

Pain is difficult to measure or assess in young infants, and, while many were in obvious pain, screaming with the knees drawn up, some lay quietly The only evidence of pain has been a slight restlessness and increase in pallor, associated with a hardening of the lump under the palpating hand Pallor is very common, not often mentioned in reports, and might indeed be added to the tetrad

Rectal bleeding was found in 161 out of 190 cases (84 7%) In 184 cases a mass was palpable in 157 (85 5%), either abdominally or per rectum

In 882 published cases, we have noted that blood was present in 80% and an abdominal mass in 73% The apex was felt per rectum in 17%

In our series, a palpable mass was found per rectum in 28 cases (10 5%), and in one case, no less than 5 in had emerged from the anus, the apex being the ileocæcal valve This was reduced and the child recovered The mortality-rate for those cases where the apex was palpable in the rectum is slightly higher than that for the whole series

Types

Intussusceptions may be divided into groups, the nomenclature of which indicates (1) the area of bowel at which invagination starts, and (2) the area of bowel receiving the invagination

Ileoileal

There were 14 cases (5 6% of the total) 7 of these required resection and 5 deaths occurred (3 resections and 2 simple reductions) This was the most lethal type, as has been noted in other series Factors leading to this high mortality-rate are the common absence of a palpable mass, often masked by abdominal distension, and the later appearance of blood in the stool, both of which contribute to delayed admission Of our 14 cases, no less than 8 had symptoms lasting over forty-eight hours Blood was present in only 7, and a mass was noted in only 3

Ileocolic

This group forms the largest of the series—84 cases (31%) Here the apex was found to have originated at points varying from $^1/_2$ to 9 in above the ileocæcal valve, and then passed onwards through the valve In 23 cases, where measurements were recorded, the average distance of the apex from the valve was $3^1/$ in Of these 84 cases, 5 required resection There were 11 deaths (13%) of which 4 had been resected

Ileocæcal

Here the valve itself forms the apex, advancing into the ascending colon, and dragging in more ileum as it advances There were 51 cases (18 9%), and 3 cases required resection There were 10 deaths (20%), including 1 which had been resected

Cæcocolic

The apex is formed by the caput cæci and, after reduction, an œdematous dimple may be noted on the most pendulous part of the cæcum This is perhaps the most difficult type of intussusception to explain, occurring as it does from the "backwater" of the most inert part of the large bowel There were 15 cases of cæcocolic intussusception—5 6% of the series None of these required resection, and there were 3 deaths

Unclassified

Insufficient details were obtainable in these cases to be able to classify them There were 75 cases (28% of the series) 4 cases required resection and out of 12 deaths (16%), 2 had been resected

Compound (or Ileo-ileocæcal)

Here an ileoileo intussusception stops at the ileocæcal valve, and the valve then advances, adding two new layers to the three layers of the original ileoileal type It might well be thought that with the larger intussusceptum, earlier symptoms and earlier strangulation would occur In fact, of the 10 cases in this series, only 3 were admitted with histories under forty-eight hours, 3 cases required resection, and 1 died after simple reduction

Multiple

There were 2 cases with separate intussusceptions, 1 has been mentioned, and the other was an ileoileal intussusception, entirely separate from an ileocolic intussusception

Management

Since Hutchinson performed the first recorded operative reduction in a child in 1871, this has been the standard procedure in many centres throughout the world In an endeavour to reduce the high mortality, methods of reduction by hydrostatic pressure were developed Hirschsprung (1905) recorded a series of 107 cases, with a mortality of 35%, after hydrostatic reduction, in other authors' hands, the operative mortality at this time was in the region of 90%

Since then, the mortality has been reduced for both operative and non-operative methods of reduction

TABLE II—MANAGEMENT

—	Cases	Deaths
No treatment possible (child in extremis)	5	5
Spontaneous reduction	6	1•
Closed manipulation	2	0
Successful reduction by barium enema	5	0
Laparotomy and reduction	229	29 (*12 7%*)
Laparotomy and resection	22	10 (*45 4%*)
Appendicectomy at time of reduction	*34*	1
Meckel s diverticulum forming apex		
Left in situ	2	1
Excised	2	1

• Died on third day Necropsy revealed recent ileoileal intussusception

Hipsley (1926) recorded a series of 100 cases treated initially by hydrostatic pressure, and operation if this failed, with a mortality of 5% His cases had an average length of history of only seventeen hours In more recent years, comparable results have been recorded for cases of less than twenty-four hours' duration, treated either by operation or hydrostatic pressure In our series, cases seen within twenty-four hours of the onset show a mortality of 6 2%

In this hospital, in the thirty-year period under review, the management has been mainly surgical until recent years (table II)

5 children were in extremis on arrival 1 had been ill for ten days, 1 for seven days, and in the other 3 no accurate history was obtainable

Judging by the signs and symptoms, 6 cases had undergone spontaneous reduction In 2 of these, evidence of recent reduction was obtained at laparotomy

2 cases were reduced under anæsthesia, using a method of combined abdominal and rectal manipulation without laparotomy This method might be dangerous in unskilled hands, particularly in cases with a history of over twenty-four hours, and, if there is any doubt about the reduction, laparotomy must still be done

Laparotomy and reduction were performed in 229 cases (85%) with a mortality of 12 7% Reduction was achieved in some cases with considerably difficulty, and serosal or seromuscular splits were required for repair

Resection proved necessary in 22 cases (8 2% of the total), with a mortality of 45% In these 22 cases, the average length of history was fifty-seven hours, and in only 3 cases was the history less than twenty-four hours This brings out again the need for early diagnosis A careful and quick resection is preferable to a prolonged attempt at closed reduction, and, in our operative records, where "great difficulty" or "serosal splits repaired" have been mentioned, the mortality has been higher Experience and judgment are two essential prerequisites in determining when to abandon attempts at reduction and resort to resection

The procedure for dealing with irreducible intussusceptions in seriously ill children remains a problem Gross (1953), Bentley (1954), and Jones (1953) have advocated a two-stage procedure, the first stage being exteriorisation, with or without suture of the loops, and the second stage being closure of the ileostomy All writers stress the importance of carrying out the second stage at about forty-eight hours, or as soon as possible after this

In our series, exteriorisation was carried out only once, in a severely ill child of 4 months with a ninety-six-hour history This child, operated on in 1940, died four hours after operation

A Witzel proximal ileostomy was carried out once in a child who was grossly obstructed because of a compound intussusception of seventy-two hours' duration which required resection The child made a satisfactory recovery This procedure, which we are using much more often in adult cases of obstruction and ileus, seems to be a useful manœuvre in the grossly obstructed child in order to decompress the dilated bowel and spare the anastomosis

We have no experience of other operative procedures for the irreducible intussusception, and there are no cases in this series A short-circuit ileotransverse colostomy, leaving the intussusception to slough and be passed per rectum, has been suggested, but this leaves a gangrenous length of bowel in the abdomen of an already sick child, with the danger of peritonitis from leakage between the entering loop and sheath Incision of the sheath to aid reduction, or to enable the intussusceptum to be excised, involves suturing œdematous and congested bowel, and has the risk of contamination through the open bowel lumen Both these procedures offer little, if any, saving of time over resection and anastomosis, and, where time is important because life is in danger, we would advocate exteriorisation and temporary ileostomy

Appendicectomy was performed at the time of reduction in 34 cases the 1 death was probably unrelated to the additional surgical procedure In some cases there is frank gangrene of this organ—a most vital indication for its removal In many others, however, the appendix shows some œdema and a greater or lesser degree of congestion—changes, in fact, similar to those in the bowel wall in the region of the reduced apex These changes will probably subside in the appendix just as they do in the bowel, and it seems illogical to remove this organ, having reduced one intussusception, only to leave another miniature one in the buried appendix stump

In 4 cases an inverted Meckel's diverticulum formed the apex Meckel's diverticula are usually stated to be the cause of intussusceptions in older children The ages, however, of these 4 children were 7, 18, 24, and 30 months If the intussusception is reducible, the question of removal arises again This is perhaps a more difficult problem Local removal of a diverticulum forming the apex will involve sewing œdematous and congested bowel and, provided viability is assured, it would seem safer to leave this abnormality In 2 cases in this series the diverticulum was left in situ, there was 1 death from peritonitis due to perforation of the diverticulum One diverticulum was excised locally and the child did well, one was irreducible and was removed by hemicolectomy The risk of recurrence after leaving a reduced Meckel's diverticulum must exist, but its incidence can only be assessed by experience with a larger number of cases than we have been able to obtain

Recurrences

10 cases have recurred, at very variable intervals after the first operation (table III)

Any type of intussusception may recur and, in 8 of the 10 cases, the second intussusception was of the same type as the first In case 6 (table III), where accurate measurements were made, the apex arose from exactly the same point on both occasions Apart from the recurrence caused by the inverted appendix stump, no causative lesion was noted in the bowel wall to explain this complication

Deliberate fixation has not been practised in this series, apart from case 5 in which a cæcocolic intussusception recurred and cæcopexy was done after the second reduction

This recurrence-rate of 3 8% compares with that of Strang (1959) who recorded 3% recurrences

Radiology

We do not propose to discuss the interpretation of straight X-rays of the abdomen, which can be of considerable use in some cases, but rather the uses of barium enemas as a means of diagnosis and a means of reduction

The use of barium enemas for reduction had not been a routine procedure in this hospital until a few years ago Since then, cases have been referred only sporadically, and these have been dealt with by any member of the radiological staff who happened to be available, whether senior or junior Hence our results cannot be compared with those from centres where systematic selection was practised, and where reduction was carried out by one interested and experienced radiologist

Barium enema has been carried out 28 times in this series In 13 cases, it was used for diagnosis only The remaining 15 cases, where a definite attempt at reduction was made, were unselected as regards age or length of history, and, in fact, no less than 8 had a history of over thirty-six hours 5 were reduced, and in 10 reduction was unsuccessful, although in these 10 cases partial reduction was achieved leading to shorter and easier intra-abdominal manipulation This gives a one-in-three chance of success for this procedure, whereas Hipsley (1926) managed to reduce 62 out of a consecutive 100 cases Zachary (1955) had a 70% success-rate out of 40 cases with a history of less than twenty-four hours, and 3 out of 12 with longer histories

Since the period under review in this series, this method has been used much more frequently and with gratifying results We now advocate that this method be given a trial in those cases where the child is in good general condition and has a short history (cases with a longer history may be included where a chronic or recurring intussusception is suspected) Barium enema is indicated for cases in which anæsthesia is hazardous, because of concomitant disease

Perforation of the bowel has not been met in this series, and there have been very few recorded cases, except when the head of pressure has been allowed to rise above three feet of barium Other disadvantages have been stated to be an unwarranted delay in operation (although this may be reduced to a minimum), and the danger of missing an incomplete reduction or an intussusception above the ileocæcal valve

In spite of these disadvantages, the use of barium enema is a very valuable method in skilled radiological hands The only real disadvantage met is that a colon loaded with barium adds to the difficulties of resection should this subsequently prove necessary, and retards a smooth convalescence after operation With careful selection, this disadvantage is minimised

Mortality

Of the 45 deaths in this series, no less than 32 were within twenty-four hours of operation, and in only 10 of these had resection been necessary In many cases necropsies were not performed, but we could safely attribute death partly to the effect of surgery on children who were dehydrated and in electrolyte imbalance 2 were in extremis and died before admission to the ward

The mortality has been steadily decreasing, and in the last decade of this series, out of 9 deaths, there were none with a history of under twenty-four hours' duration, 5 had a history of forty-eight hours or over

There are two main factors contributing to this fall in mortality—more modern anæsthesia and a better understanding of fluid and electrolyte balance We would stress the importance of unhurried and adequate rehydration by intravenous fluid before these cases are submitted to operation

Summary

The incidence and management of 269 consecutive cases of intussusception in childhood occurring over a thirty-year period are reviewed

TABLE III—DETAILS OF RECURRENCES

Case	Age (months)	Sex	First intussusception		Second intussusception		
			Date of admission	Operative notes	Time of recurrence	Operative notes	Result
1	10	M	April 1931	Laparotomy on admission Spontaneous reduction with signs of recent ileoileal intussusception	? 3 days	Died on third day Recent ileoileal intussusception found at autopsy	D
2	12	M	Dec 1932	Laparotomy and reduction of unclassified enterocolic intussusception	3 mos	Laparotomy and reduction of a similar intussusception	A
3	8	M	April 1934	Laparotomy and reduction of unclassified intussusception	5 mos	Laparotomy and reduction of a similar intussusception	A
4	19	M	Oct 1935	Laparotomy and reduction of unclassified enterocolic intussusception	25 mos	Laparotomy and reduction of ileocæcal intussusception	A
5	36	F	Dec 1939	Laparotomy and reduction of cæcocolic intussusception	7 days	Laparotomy and reduction of recurrent cæcocolic intussusception Cæcopexy Died 2 weeks later of gastroenteritis	D
6	11	M	July 1941	Laparotomy and reduction of ileocolic intussusception Apex 8 in. above ileocæcal valve	6 mos	Laparotomy and reduction of ileoileal intussusception with apex 8 in above the ileocæcal valve	A
7	6	F	May 1946	Laparotomy and reduction of ileocæcal intussusception with difficulty	? 9 days	Died on 9th day Necropsy—acute jejunojejunal intussusception	D
8	14	M	April 1950	Laparotomy and reduction of ileocolic intussusception	12 mos	Laparotomy and reduction of recurrent ileocolic intussusception	A
9	10	M	Sept 1956	Laparotomy and reduction of ileocolic intussusception Appendicectomy	3 days	Laparotomy and reduction of cæcocolic intussusception Appendix stump forming the apex. Readmitted Jan , 1957, with typical history and abdominal mass Barium enema—no abnormality Presumed spontaneous reduction	A
10	4	M	Nov 1957	Laparotomy and reduction of ileocæcal intussusception	1 mo	Laparotomy and reduction of recurrent ileocæcal intussusception with difficulty	A

D = died A = alive.

Factors affecting the mortality-rate are discussed, and a strong plea is made for earlier reference to hospital of any suspicious case.

The mortality-rate fell, from 17·6% in the first decade to 8·9% in the third decade, and we attribute this to better resuscitative and anæsthetic techniques. This fall in mortality has been achieved in spite of an increase in the length of history before reference to hospital.

The ætiology is discussed, and attention drawn to infective and anatomical factors.

The series has been broken down into anatomical types, and their incidence, management, and mortality are described. The high mortality of ileoileal intussusceptions is noted and reasons for this suggested.

Suggestions are made for dealing with the irreducible intussusception. Resection and anastomosis, carried out before prolonged attempts at reduction have produced shock and bowel injury, is the method of choice. Exteriorisation and ileostomy are suggested for the poor-risk case. Other operative procedures are deprecated.

The place for appendicectomy and Meckel's diverticulectomy at the time of reduction is discussed.

The recurrence-rate is reviewed.

The use of barium enema for reduction is advocated in selected early cases with a history of under twenty-four hours and in good general condition.

We should like to thank the many consultants, past and present, under whom these children have been admitted, and the resident staff whose note-keeping has made this review possible. We are particularly grateful to Mr C. Vincent Patrick, Dr H. Everley Jones, and Dr A. P. Booth for helpful advice and criticism.

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ANTIBODIES TO THYROGLOBULIN IN PATIENTS WITH THYROTOXICOSIS TREATED WITH RADIOACTIVE IODINE

C. R. BLAGG
M.B. Leeds, M.R.C.P.

RESEARCH FELLOW, DEPARTMENT OF MEDICINE,
THE GENERAL INFIRMARY, LEEDS

RADIOACTIVE iodine is now an accepted agent in the treatment of thyrotoxicosis in three groups of patients—those over the age of forty, those who have relapsed after partial thyroidectomy, and those who are unsuitable for surgery because of coexistent disease. The only drawback of this treatment, apart from the still undetermined risk of development of thyroid malignancy or leukæmia, is the relatively high incidence of hypothyroidism which results.

According to published series, 5–25% of patients become hypothyroid. In the British Isles, the usual incidence is about 12%, one year after treatment (Blomfield et al. 1959, Macgregor 1960). Macgregor (1960) reports that the incidence of hypothyroidism in their patients had risen to 17% three years after treatment and Werner et al. (1957) also recorded the continued development of hypothyroidism for years after treatment. Larsson (1955), however, has shown that thyroid function is at its lowest six to eight weeks after therapy. It would, therefore, appear that the development of hypothyroidism more than a few months after treatment is not directly due to a radiation effect.

The toxic thyroid gland is frequently the site of lymphocytic infiltration, and, after surgical thyroidectomy, there is a relationship between the severity of these histological changes and the incidence of postoperative myxœdema (Whitesell and Black 1949, Greene 1950, 1953). More recently, it has been shown that anti-thyroid antibodies are found in about 60% of patients with untreated thyrotoxicosis (Roitt and Doniach 1958). Smart and Owen (1960) report that they have found these antibodies in 80% of patients with myxœdema following surgery, and suggest that the presence of antibodies in patients with thyrotoxicosis "should probably therefore be accorded clinical significance, at least in deciding the most appropriate form of treatment."

Studies have been reported on only a few patients after treatment with radioactive iodine (Blizzard et al. 1959, Cline et al. 1959). This paper reports the findings in a larger series.

Subjects and Method

Patients with thyrotoxicosis, who had been referred to the isotope department for treatment with ^{131}I, were investigated. Titres of autoantibodies against thyroglobulin were estimated by a modification of the tanned-cell agglutination principle of Boyden (1951), as described by Owen and Smart (1958). In all estimations, known positive and negative sera were included among the controls.

Serum was studied from:

(1) 102 patients with thyrotoxicosis, confirmed by tracer studies, attending for treatment with ^{131}I.

(2) 103 patients attending the follow-up clinic who had been treated with ^{131}I and were subsequently euthyroid. All the patients had been treated at least one year before this investigation.

(3) 58 patients attending the follow-up clinic after treatment with ^{131}I, diagnosed clinically as being hypothyroid—confirmed by tracer studies, blood-cholesterol, electrocardiogram, or basal metabolic rate—who required replacement therapy.

The dosage of ^{131}I used was intended to give 7000–10,000r to the thyroid gland in fourteen days.

Results

The results of clinical follow-up of 67 patients treated with ^{131}I more than six years before this investigation are shown in table I. The incidence of hypothyroidism continues for years after the last dose of ^{131}I. Blomfield et al. (1959) and our own unpublished observations confirm that the development of hypothyroidism cannot be closely related to the size or nature of the thyroid gland, or to any of the physical characteristics usually measured in prescribing treatment with ^{131}I.

Autoantibodies were demonstrated in 53 (52%) of 102 patients with thyrotoxicosis before treatment with ^{131}I, and in 57 (55%) of 103 who were euthyroid for a minimum

TABLE I—THE CONTINUED DEVELOPMENT OF HYPOTHYROIDISM IN 67 PATIENTS TREATED WITH ^{131}I AND FOLLOWED UP OVER A 6-YEAR PERIOD

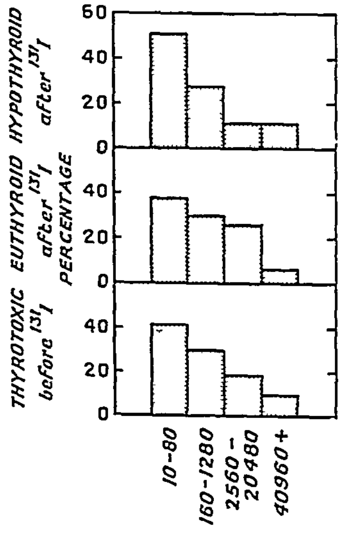
Years since last ^{131}I therapy	Total no. of patients becoming hypothyroid	% of total
0–1	8	12
1–2	10	15
2–3	12	18
3–4	13	19
4–5	[illegible]	[illegible]
5–6	[illegible]	[illegible]

TABLE II—PRESENCE OF ANTI-THYROID ANTIBODIES IN SERUM OF PATIENTS BEFORE AND AFTER TREATMENT WITH ^{131}I

—	No of patients	No with antibodies	% with antibodies
Pretreatment	102	53	52
Euthyroid after ^{131}I	103	57	55
Hypothyroid after ^{131}I	58	45	77

of one year after the last treatment Of 58 patients with post-therapy hypothyroidism, however, 45 (77%) showed the presence of autoantibodies (table II) This difference is statistically significant ($0\ 001 < P < 0\ 01$) Separation of the hypothyroid patients into two groups—34 who developed hypothyroidism within one year of treatment, and 24 who became hypothyroid more than one year after treatment—shows no difference in the incidence of autoantibodies (76% and 78%)

Roitt and Doniach (1958) reported that in patients with untreated thyrotoxicosis, the titres were nearly always low —i e, 1/10–1/1520 in approximately 90%, as opposed to the high titres (1/10,240–1/168 million) found in patients with Hashimoto's thyroiditis No significant difference was found in the mean titres of autoantibody in the three groups in the present series, and they were not significantly higher in the patients developing hypothyroidism (see figure)



Concentration of autoantibodies to thyroglobulin in serum of patients before and after ^{131}I therapy

Discussion

These results suggest that the development of hypothyroidism following treatment with ^{131}I is associated indirectly with the autoimmunological processes recently described in thyroid disease (Roitt and Doniach 1960) This might be expected in the light of the relationship between histological lymphocytic infiltration of the thyroid gland and the development of myxœdema after surgery (Whitesell and Black 1949, Greene 1950, 1953), the correlation between the presence of anti-thyroid antibodies and the finding of mild Hashimoto-like changes in the thyroid glands of subjects without overt thyroid disease (Goudie et al 1959), and the recent demonstration that 80% of patients with post-operative myxœdema have demonstrable thyroid autoantibodies (Smart and Owen 1960) as compared with 50–60% of those with untreated thyrotoxicosis

Hall et al (1960) have shown that the disposition to develop thyroid autoantibodies may be genetically determined, and sibs of patients with thyroid disease may show the presence of autoantibodies without clinically apparent thyroid disease Anti-thyroid antibodies are also found in 6–18% of patients without clinical evidence of thyroid disease (Goudie et al 1959, Hackett et al 1960)

Complement-fixing autoantibody, present in the sera of about 40% of patients with untreated thyrotoxicosis and directed against an antigen found in the microsome fraction after differential centrifugation of thyrotoxic-gland extract (Roitt and Doniach 1958), was not estimated in the present study However, Pulvertaft et al (1959) have shown that the cytotoxic effects of sera from patients with Hashimoto's thyroiditis on thyroid cells in tissue culture appear to be due to a factor other than either the complement-fixing autoantibody or the antibody to thyroglobulin

In the light of these facts and the generally low titres of autoantibodies in all groups of patients in the present series, it would seem that the antibodies themselves are not directly responsible for the development of hypothyroidism Their presence may indicate some underlying abnormality, disposing in some cases to ultimate destruction of the thyroid gland It would, therefore, seem unreasonable at present to withhold such a simple and satisfactory method of treating thyrotoxicosis from patients with a low titre of circulating autoantibodies, particularly as most patients treated are over the age of forty, and, if hypothyroidism should develop, replacement therapy with thyroxine is cheap, easy, and safe

Patients with Hashimoto's thyroiditis sometimes first attend with thyrotoxicosis (Vaux 1938) The typical hard, horseshoe-shaped goitre of Hashimoto's thyroiditis soon develops and the level of autoantibodies rises greatly (Doniach et al 1959) It should be easy to distinguish these cases clinically, and by the use of the precipitin test (Doniach and Roitt 1957) This is a simple and relatively insensitive test that is only positive in cases with a high titre of autoantibodies against thyroglobulin No such case is described in the present series, but it would seem reasonable, if possible, to avoid both surgery and ^{131}I in such patients, because of the risk of causing hypothyroidism Such patients may, however, be difficult to treat with anti-thyroid drugs because these may cause further enlargement of the goitre

Summary

Study of the serum of patients before and after treatment of thyrotoxicosis with radioactive iodine showed a significantly higher incidence of circulating anti-thyroid antibodies in those who had developed hypothyroidism Antibody was found in 52% of patients before treatment, in 55% of patients who were euthyroid at least one year after treatment, and in 77% of patients who had become hypothyroid after treatment The titre of antibodies was low in most cases in each group

An autoimmune mechanism may possibly be indirectly associated with the development of hypothyroidism occurring years after treatment with ^{131}I, but the presence of a low titre of anti-thyroid antibodies in patients with thyrotoxicosis is not to be regarded in itself as an indication to withhold treatment with radioactive iodine

The precipitin reaction should distinguish between hyperthyroid patients and those few patients with early Hashimoto's thyroiditis who present with thyrotoxicosis

I wish to thank Prof R E Tunbridge for his advice and encouragement, Dr S G Owen for advice on the estimations, and Miss V Grayson for her assistance with this work

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PROTEIN-LOSING ENTEROPATHY IN THE SPRUE SYNDROME

R A PARKINS
M B Lond , M R C P

SENIOR MEDICAL REGISTRAR, CHARING CROSS HOSPITAL, LONDON, W C 2

Green and Wollaeger (1958) have criticised the terms 'idiopathic steatorrhœa" and "malabsorption syndrome" because they emphasise only one aspect of the malabsorption which affects carbohydrate, protein, vitamins, water, and many substances other than fat The alternative names of "tropical and non-tropical sprue" or "the sprue syndrome" are preferable

In a survey of non-tropical sprue in the United States, Green and Wollaeger found hypoproteinæmia with the total serum-proteins below 6 0 g per 100 ml in 70% of their patients, while the serum-albumin levels were less than 3 5 g per 100 ml in 60% This hypoproteinæmia and the muscle-wasting so often seen in this condition have been attributed to protein malabsorption The earlier studies of Thaysen (1926), however, showed that small fæcal nitrogen losses, when compared with those of fats, were a diagnostic feature in idiopathic steatorrhœa Comfort et al (1953) found that the majority of their patients with sprue had abnormal fæcal nitrogen levels, but could not find any relation between the fæcal fat and fæcal nitrogen excretions On the other hand, Cooke et al (1953) found a significant relationship between the fæcal fat and fæcal nitrogen levels in ten cases of idiopathic steatorrhœa

These observations suggest a significant difference between the metabolism of fat and of protein in the sprue syndrome Alternatively, the discrepancy could be explained by leakage of protein into the gastrointestinal tract—"exudative enteropathy" or "protein-losing enteropathy" (Gordon 1959, Schwartz and Jarnum 1959) A number of workers have demonstrated this protein-loss in hypertrophic gastritis, Crohn's disease, ulcerative colitis, and other gastrointestinal diseases (Citrin et al 1957, Steinfield et al 1957, Gordon 1959, Holman et al 1959, Jarnum and Schwartz 1960) The discovery by Paulley, in 1954, of atrophic changes in the mucosa of the small intestine of patients with idiopathic steatorrhœa suggests a possible origin for protein-losing enteropathy Similar histological changes have been shown in patients with cœliac disease by Sakula and Shiner (1957), and in tropical sprue by Butterworth and Perez-Santiago (1958)

Gordon (1959) has described an ingenious technique to demonstrate and to measure this increased intestinal permeability He used a polyvinylpyrrolidone with a molecular weight about that of albumin When labelled with radio-iodine this polymer resists the action of digestive juices After intravenous injection increased intestinal permeability is indicated by the finding of excessive radioactivity in the fæces Using this technique, Schwartz and Jarnum (1959) demonstrated protein-losing enteropathy in a patient with hypoproteinæmia due to sprue

The object of this investigation was to determine if protein-losing enteropathy occurred in patients with the sprue syndrome, and to correlate this enteropathy with clinical and histological findings, and with the results of protein-absorption tests

Patients

Eleven patients were studied One was a child with cœliac disease Two adults had symptoms dating back to childhood, and were thought to have adult cœliac disease Two developed symptoms for the first time while in the tropics, but had relapses after returning to Britain, although initially thought to have tropical sprue, some features suggest that they may be cases of idiopathic steatorrhœa or non-tropical sprue, and belong to the same group as the other six patients in the series Seven of the eleven patients responded to a gluten-free diet, and may, alternatively, be classed as cases of gluten enteropathy The term "sprue syndrome" will be used for this whole group of conditions

The diagnosis was established by the history, the finding of a fæcal fat excretion in excess of 6 g daily, impaired glucose absorption, and radiological abnormality of the mucosal pattern of the small intestine Jejunal biopsies in each patient showed atrophic changes in the mucosa

Methods

All the patients were asked about weight-loss in the months before admission Routine estimations of the hæmoglobin, serum-proteins, and albumin levels were made Fæcal fat was calculated as the mean daily excretion during a 4-day collection, while receiving a 70 g fat diet

Jejunal Biopsies

Jejunal biopsies were obtained by the capsule method of Crosby and Kugler (1957) Biopsy specimens varied in size from 7 to 15 mm in diameter After careful orientation, they were fixed in formal-saline and embedded in wax Accurately cut perpendicular sections were stained with hæmatoxylin and eosin Histological changes in the epithelium, the size and shape of the villi, and the amount of cellular infiltration were assessed, without knowledge of the clinical findings

Radio-iodine-labelled Albumin

Albumin labelled with radio-iodine (^{131}I-albumin) was used to assess the efficiency of absorption of ingested protein The method was that described by Chinn et al (1953) ^{131}I albumin was prepared by the method of Veall et al (1955) The dose, containing approximately 20 μC of radioactivity, was given to the fasting patient with a carrier of gelatine, 0 5 g per kg body-weight For the 24 hours before the test, and for the succeeding 4 days, potassium iodide 60 mg three times daily was given to prevent thyroid uptake of radio-iodine All the fæces passed in the 4 days after the dose were collected and the radioactivity assayed by comparison with a known fraction of the dose administered Radioactivity was measured in a multiple component Geiger-Muller ring counter connected to an 'Ekco Autoscaler' Results were expressed as the percentage of the administered dose excreted in the stools during the 4-day collection Normal excretion was less than 5

Radio-iodine-labelled Polyvinylpyrrolidone

This material was obtained from the United States, through the courtesy of Dr Robert S Gordon

Before injection, the solution was dialysed to exclude contamination by unbound radioactive iodine or by polymer of low molecular weight After being autoclaved, a dose of [illegible] 10 μC was given intravenously [illegible]

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CLINICAL DETAILS OF PATIENTS, RESULTS OF ISOTOPE STUDIES, AND HISTOLOGICAL GRADINGS OF BIOPSY SPECIMENS

—	Case no										
	1	2	3	4	5	6	7	8	9	10	11
Sex	F	F	M	F	M	F	M	F	F	F	M
Age (years)	65	46	44	29	58	50	49	18	$1^{10}/_{12}$	34	58
Symptoms	D, T	T	D, H	D	D, B	D, S	D	S	S	D	D, B
Weight loss (kg)	6 0	3 2	9 7	6 2	6 4	14 5	6 0	38 7*	8 7*	3 7	8 2
Hæmoglobin (g per 100 ml)	10 6	12 1	10 3	9 3	11 2	9 8	13 1	13 0	8 3	8 3	14 5
Type of anæmia	M	M	M	M	M	M	Nil	F	F	F	M
Serum albumin (g per 100 ml)	4 7	3 5	4 0	3 8	4 0	3 6	4 9	4 8	5 6	2 7	3 0
Fæcal fat (g per 24 hours)	21 3	29 0	16 4	20 7	30 0	10 0	25 0	13 3	18 0	10 4	9 4% †
Biopsy											
Epithelium	2	3	3	3	3	0	0	2–3	3	3	3
Villi	1	3	3	3	3	1	1	3	3	3	3
Cellular infiltration	2	2	2	2	3	1	3	3	2	3	3
Fæcal ^{131}I albumin (%)	1 3	6 3	0 6	1 2	14 9	0 3	1 6	0 9	3 8	1 8	5 5
Fæcal ^{131}I P V P (%)	3 6	1 4	2 1	0 8	3 0	0 3	0 7	1 0	6 7	0 8 1 4	0 9
Gluten sensitivity	Yes	?	Yes	?	Yes	?	Yes	Yes	Yes	?	Yes
Final diagnosis	I S	I S	?S	I S	I S	A	I S	C	C	A	?A

T = tetany D = diarrhœa H = hæmorrhage S = stunting B = bone pain M = megaloblastic F = iron deficient C = cœliac A = adult cœliac S = tropical sprue I S = idiopathic steatorrhœa * = actual body-weight † = ^{131}I-fat excretion ^{131}I P V P = radio iodine labelled polyvinylpyrrolidone

known fraction of the dose administered Fæces were collected for the next 4 days and the radioactivity assayed in the same way as for the ^{131}I-albumin The results were expressed as the percentage of the administered dose found in the fæcal collection Gordon (1959) states that the fæcal excretion of radio-iodine-labelled polyvinylpyrrolidone (^{131}I-P V P) in forty-one normal subjects was less than 1 5% of the dose In ten normal subjects examined by me, the fæcal excretion was found to be less than 1%

A maximum dose of 1 μC was used for each of the two tests for the one child in the series The stools were homogenised, and aliquots counted in a thallium-activated sodium-iodide crystal-well-type scintillation counter connected to an Ekco autoscaler

Care was taken to exclude urinary contamination of the fæcal collections

Results

The clinical details of the eleven patients, the results of the isotope studies, and the histological gradings are summarised in the table

Jejunal Biopsies

The histological changes in the intestinal mucosa were assessed under three headings

1 The orderliness and cellular height of the mucosal epithelium

2 The height, shape, width, and fusion of the villi, and the depth of the crypts

3 The total thickness of the mucosa glandular layer and the degree of cellular infiltration

Changes were graded from 0 to 3 (0=normal, 3=severe) The biopsy specimens were graded without knowledge of the clinical details

In patients 2 and 7, the biopsies were repeated after an interval of 2 and 6 months respectively, and no significant changes were observed

Radio-iodine-labelled Albumin Absorption

Three patients excreted an abnormal percentage of the administered dose in the fæcal collection case 2, 6 3%, case 5, 14 9%, and case 11, 5 5% Each had considerable steatorrhœa at the time of testing and their fæcal fat excretions were the highest in the series

The fæcal losses of ^{131}I-albumin, however, were not closely related to the severity of the disease or the steatorrhœa when the whole group was considered, nor was there a relationship between the level of the total serum-proteins or serum-albumin and the fæcal excretion of radioactivity

Radio-iodine-labelled Polyvinylpyrrolidone

Four of the eleven subjects excreted more than 1 5% of the administered dose in the 4-day fæcal collection (case 1, 3 6%, case 3, 2 1%, case 5, 3 0%, and case 9, 6 7%)

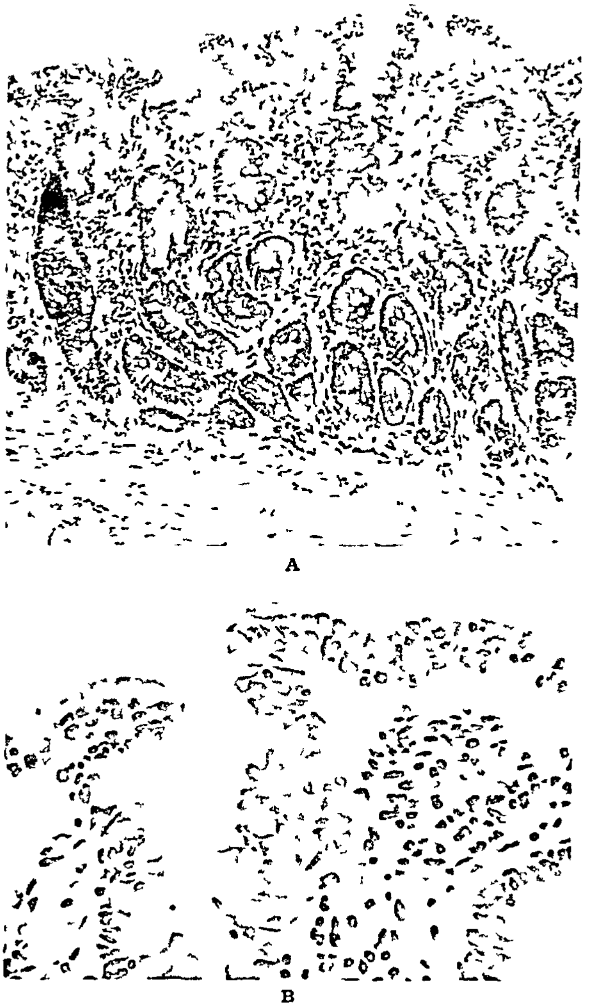

Fig 1, A and B—Jejunal biopsy (case 5), before gluten-free diet. (A×30, B×120)

The fæcal excretion of the tracer could not be related to the clinical severity of the disease, nor to the weight-loss in the months preceding the investigation.

There was no relationship between the excretion of ^{131}I-P.V.P. and the level of the serum-albumin, the total serum-proteins, or the fæcal fat excretion. Similarly there was no correlation between the fæcal losses of ^{131}I-albumin and ^{131}I-P.V.P.

Only case 5 had a high elimination of both tracer substances; despite this, the serum-albumin and total proteins remained just below the normal range. His steatorrhœa was severe, and he was the only patient in the series with bone pain.

Three of the four patients excreting an abnormal percentage of ^{131}I-P.V.P. showed severe abnormality of the jejunal mucosa, and each responded satisfactorily to a gluten-free diet.

Illustrative Case-record

A man, aged 58 (case 5). In 1952, he had diarrhœa with pale frothy stools, and soreness of the tongue. There was no past history of bowel disturbance or of residence in the tropics. Investigation at that time showed steatorrhœa and a megaloblastic anæmia. Non-tropical sprue was diagnosed and treatment was begun with folic acid and a low-fat diet. Bouts of intermittent diarrhœa persisted until 1959, when he attended here with bone pain and a recurrence of diarrhœa, having lost 14 lb. (6·3 kg.) in the preceding year.

There was no abnormality, other than weight-loss and bone-tenderness. He was found to have a mild microcytic anæmia with hæmoglobin 12 g. per 100 ml. (81%). Serum-calcium 3·6 mEq. per litre, serum-phosphate 3·1 mg. per 100 ml.; serum-proteins 5·7 g., albumin 4·0 g., globulin 1·7 g. The glucose-absorption curve was flat, and the fæcal fat excretion 30 g. daily. Radiologically, the small intestine had an abnormal mucosal pattern. A jejunal biopsy confirmed that there was severe villous atrophy (fig. 1). The fæcal excretion of ^{131}I-albumin was raised, 14·9% of the administered dose being lost in the 4-day collection. The fæcal loss of ^{131}I-P.V.P. was also high, 3·0% of the dose being found in the 4-day period.

The response to a gluten-free diet was dramatic; within 2 weeks, the patient was passing formed stools for the first time in 7 years.

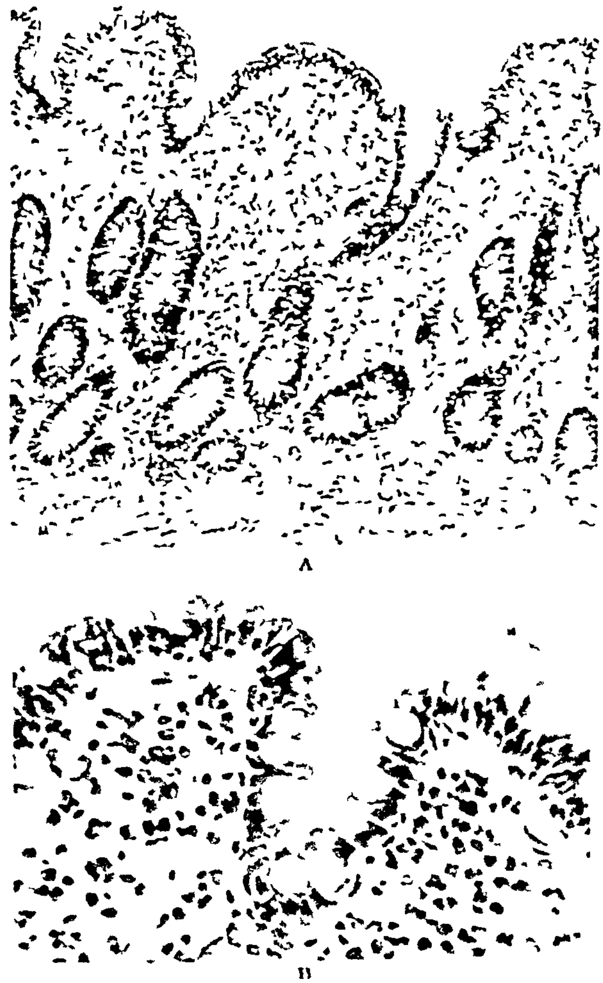

Fig. 2—A and B—Jejunal biopsy from case of cœliac disease kept in remission for 2 years with a gluten-free diet (case 8). (A ×30; B ×120.)

Discussion

This investigation shows that protein-losing enteropathy does occur in some patients suffering from the sprue syndrome. The present study, however, fails to show any relationship between the level of the serum-albumin and the fæcal losses of the ^{131}I-P.V.P., such as was found by Gordon (1959), in his studies of patients with idiopathic hypercatabolic hypoproteinæmia.

The one patient (case 10) in the present series with severe hypoproteinæmia on two occasions had losses of ^{131}I-P.V.P. within the normal range.

The lack of correlation between the appearances of the jejunal mucosa and the losses of ^{131}I-P.V.P. suggest that these histological changes are not responsible for the increased intestinal permeability. Culver et al. (1959) report that they were unable to find any constant relation between the severity of malabsorption and the histological changes seen on jejunal biopsy from patients with sprue. These observations, and the finding of severe grades of mucosal atrophy in cœliac disease after long-lasting remission on a gluten-free diet (fig. 2), indicate that the factor responsible for the increased permeability and malabsorption is not the histologically visible lesion but is possibly an enzymal defect of the mucosal cell.

The lack of correlation between the absorption of ^{131}I-albumin and the fæcal losses of ^{131}I-P.V.P. seems to indicate that the processes of protein absorption and protein-losing enteropathy are independent.

This study suggests that the protein disturbances of sprue are complex, and not solely attributable to protein malabsorption, or to increased intestinal permeability or even to a combination of these two processes.

Summary

Eleven patients with the sprue syndrome have been investigated with radioactive-isotope tracers to detect the presence of protein malabsorption and protein-losing enteropathy.

Protein malabsorption was detected in three, and protein-losing enteropathy in four. No correlation could be found between these defects of protein metabolism and the clinical state, nor with the level of serum-proteins, or the histological changes in the mucosa of the small intestine.

My thanks are due to the physicians of Charing Cross Hospital and to Dr. C. C. Booth [illegible] Medical School [illegible] and nurses of [illegible]

References at foot of next column

DANGEROUS GROUP-O BLOOD

A SIMPLIFIED TEST

JOHN W. LOCKYER
F.I.M.L.T.
SENIOR TECHNICIAN

GEOFFREY H. TOVEY
M.D. Brist.
MEDICAL DIRECTOR

SOUTH-WESTERN REGIONAL TRANSFUSION CENTRE, BRISTOL

SOME group-O bloods are regarded as unsuitable for emergency transfusion to recipients of other groups because their plasma contains anti-A or anti-B antibodies in critically high titre. Gardner and Tovey (1954) have described a screening test for detecting anti-A and anti-B hæmolysins and immune agglutinins, and it is generally agreed that a separate test for high-titre saline agglutinins is unnecessary, since they are almost always associated with hæmolysins (Medical Research Council 1958). The screening test recommended has the disadvantage that about 20% of group-O bloods show hæmolysins; hence there may be difficulty in supplying enough blood for emergency use. Since, however, there is evidence that only those bloods which contain a considerable amount of hæmolysin are dangerous, it has been advised that samples giving a positive result in the screening test should be further tested and labelled as unsuitable for transfusion to recipients other than O only if the hæmolysins are present at a titre greater than 1/8 (Medical Research Council 1958). In a busy laboratory such titrations may appreciably increase the volume of work, as well as introducing the need for a lysin-free complement. Winstanley et al. (1957) have shown that sera containing anti-A hæmolysins and immune agglutinins agglutinate pig red cells containing the A^P antigen, and during investigations of this reaction about one-third of these sera were found also to hæmolyse the group-A pig cells (Lockyer 1959). We undertook an investigation, therefore, to determine whether the test for dangerous group-O donors could be simplified by using group-A^P cells instead of human group A_1.

Materials

Samples of clotted and citrated blood (approximately 20 ml. in 6 ml. of acid-citrate-dextrose (A.C.D.)) were collected weekly from each of 10 pigs slaughtered at a local abattoir and stored at 4°C until required.

Grouping of pig red cells.—The pig red cells from the citrated samples were washed three times with 1·5% saline to minimise autohæmolysis (Lockyer 1959) and papainised by incubating the washed packed cells at 20°C for 5 minutes with an equal volume of Löw's papain. The cells were then washed once, diluted to an approximate 10% suspension in 1·5% saline, and incubated with an equal volume of pig anti-A serum in 3×½ in. tubes for 1 hour at 20°C. About one-third of the pig samples grouped as A^P by this technique, some weakly, some strongly. The cell suspensions showing the strongest reactions were selected as the A^P test cells.

Selection of pig anti-A sera.—One volume of a 10% suspension of washed red cells in 1·5% saline from each of the citrated samples was incubated for 1 hour at room temperature with one volume of serum from each of the 10 clotted samples. Any serum agglutinating some of the pig-cell suspensions was then shown to have come from a group-O pig and to contain anti-A^P agglutinins. The strongest reactors were stored at −20°C for grouping subsequent samples of pig cells.

Group-O sera.—The sera investigated were those from routine blood-donor sessions and were examined for hæmolysins within 24 hours of collection. Some sera were further tested after storage as whole clotted blood for 48–72 hours at 4°C.

Complement.—Fresh group-O serum, proved free of hæmolysins and low in anti-A and anti-B titre, was used. Complement activity was tested by adding the serum to an inactivated serum known to contain anti-A hæmolysins; group A_1 cells were then added to test for reactivation. Sera found to be rich in complement and free of hæmolysins were freeze-dried, stored, and reconstituted with distilled water immediately before use.

Methods

Sera from group-O donors, bled at routine blood-donor sessions, were screened for hæmolysins by the method described by Gardner and Tovey (1954). Those showing a positive result at 37°C were further tested at a dilution of 1/8 by the method recommended in the M.R.C. memorandum (Medical Research Council 1958).

All sera hæmolysing human A_1 or B cells at 37°C were further tested for anti-A^P hæmolysins by incubating equal volumes of the serum and a 10% suspension of non-papainised A^P cells in 1·5% saline in 3×½ in. tubes for 1 hour; a suspension of group-O^P cells was similarly tested as a control. To begin with these tests were carried out at 37°C, but it was found that the A^P and O^P cells showed non-specific hæmolysis at this temperature. Hæmolysis of A^P cells was specific at room temperature (about 20°C) and the routine tests for anti-A^P hæmolysins were therefore carried out at this temperature. When the sera were tested within 48 hours of collection the addition of complement was unnecessary. An equal volume of reconstituted freeze-dried serum containing complement was added to sera tested more than 48 hours after collection. The pig cells collected into A.C.D. remained satisfactory as test cells for at least 7 days when stored at 4°C.

TABLE I—INVESTIGATION OF SERA FOR HÆMOLYSINS

Total group-O sera examined	2500
Number hæmolysing human A_1 or B cells at 37°C	450 [illegible]
Number hæmolysing A_1 or B cells at a titre of 1/8	90 [illegible]
Number hæmolysing A^P cells at room temperature	105 [illegible]

Results

The results of examining 2500 group-O sera for hæmolysins are summarised in table I. Had Gardner and Tovey's screening test for hæmolysins been used, 450, or 18%, of the bloods under test would have been labelled as 'dangerous'. Only 90 of these, in fact, contained hæmolysins for human A or B cells at a titre of 1/8, and the serum from each of these samples hæmolysed pig group-A cells at room-temperature. A further 15 sera also hæmolysed the A^P cells, so that if pig group-A cells were used as a routine, 105 of the 2500 group-O bloods, or about 4%, would be labelled as "dangerous". These

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The fæcal excretion of the tracer could not be related to the clinical severity of the disease, nor to the weight-loss in the months preceding the investigation

There was no relationship between the excretion of ^{131}I-P V P and the level of the serum-albumin, the total serum-proteins, or the fæcal fat excretion Similarly there was no correlation between the fæcal losses of ^{131}I-albumin and ^{131}I-P V P

Only case 5 had a high elimination of both tracer substances, despite this, the serum-albumin and total proteins remained just below the normal range His steatorrhœa was severe, and he was the only patient in the series with bone pain

Three of the four patients excreting an abnormal percentage of ^{131}I-P V P showed severe abnormality of the jejunal mucosa, and each responded satisfactorily to a gluten-free diet

Illustrative Case-record

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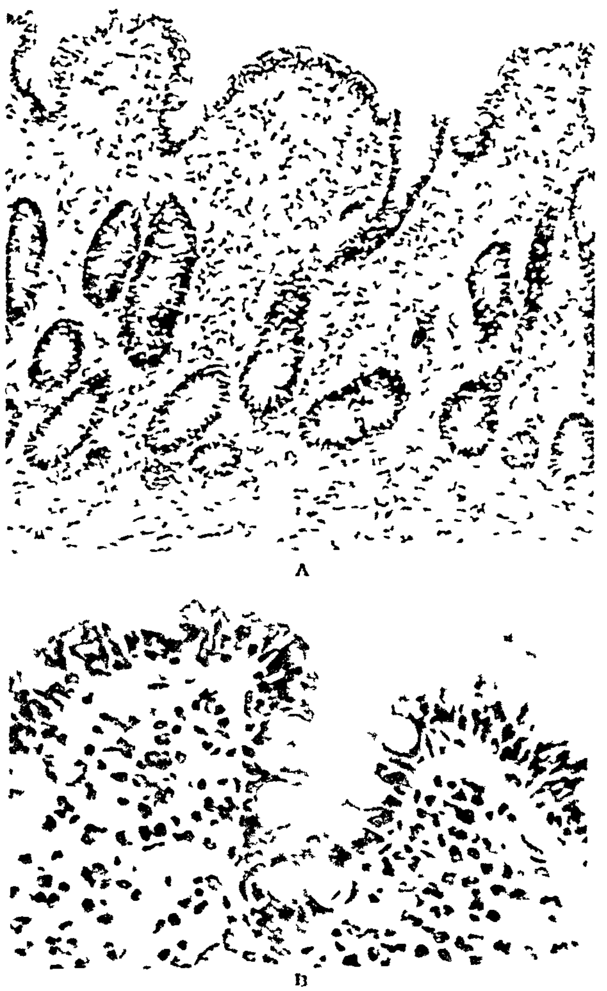

Fig 2, A and B—Jejunal biopsy from case of cœliac disease kept in remission for 2 years with a gluten-free diet (case 8) (A ×25, B ×120)

There was no abnormality, other than weight-loss and bone-tenderness He was found to have a mild microcytic anæmia with hæmoglobin 12 g per 100 ml (81%) Serum-calcium 3 6 mEq per litre, serum-phosphate 3 1 mg per 100 ml serum-proteins 5 7 g, albumin 4 0 g, globulin 1 7 g The glucose-absorption curve was flat, and the fæcal fat excretion 30 g daily Radiologically, the small intestine had an abnormal mucosal pattern A jejunal biopsy confirmed that there was severe villous atrophy (fig 1) The fæcal excretion of ^{131}I-albumin was raised 14 0% of the administered dose being lost in the 4-day collection The fæcal loss of ^{131}I-P V P was also high, 3 0% of the dose being found in the 4-day period

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Discussion

This investigation shows that protein-losing enteropathy does occur in some patients suffering from the sprue syndrome The present study, however, fails to show any relationship between the level of the serum-albumin and the fæcal losses of the ^{131}I-P V P, such as was found by Gordon (1959), in his studies of patients with idiopathic hypercatabolic hypoproteinæmia

The one patient (case 10) in the present series with severe hypoproteinæmia on two occasions had losses of ^{131}I-P V P within the normal range

The lack of correlation between the appearances of the jejunal mucosa and the losses of ^{131}I-P V P suggest that these histological changes are not responsible for the increased intestinal permeability Culver et al (1959) report that they were unable to find any constant relation between the severity of malabsorption and the histological changes seen on jejunal biopsy from patients with sprue These observations, and the finding of severe grades of mucosal atrophy in cœliac disease after long-lasting remission on a gluten-free diet (fig 2), indicate that the factor responsible for the increased permeability and malabsorption is not the histologically visible lesion but is possibly an enzymal defect of the mucosal cell

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My thanks are due to the physicians of Charing Cross Hospital, and to Dr C C Booth of the department of medicine, Postgraduate Medical School for allowing me to investigate their cases and to the sisters and nurses of these hospitals for their cooperation

References at foot of next column

attempts yielded inadequate tissue. A more exacting histologist who demanded ten glomeruli per single section would have classified more than half of the biopsy attempts as unsuccessful. Some biopsies taken with the Vim-Silverman needle contain very little cortex, presumably because the trocar and sheath are inserted a short distance into the kidney before the biopsy is taken. In a pathological kidney, with a cortex only a few millimetres thick, the specimen may consist largely of medulla.

(3) *Although dangerous complications are rare, troublesome ones are fairly common.*—Of Kark's patients, 9·8% suffered from one of four unpleasant side-effects—gross or prolonged hæmaturia, renal colic, perirenal hæmatoma, or renal infection. The discomfort following renal biopsy is one of the factors limiting its application in the nephrotic syndrome of children.

These drawbacks of the standard method of renal biopsy are far outweighed by its usefulness, but they leave considerable scope for improvement in the technique. A modification, which I described here, has proved more satisfactory in my hands than the original method of Kark and Muehrcke.

Present Method

The usual preliminary tests of platelet-count, prothrombin-time, clotting-time, bleeding-time, and blood-group are done. Premedication is given to some adults; all children are heavily sedated with a "cocktail" of pethidine, promethazine, and promazine which has proved highly successful in allaying anxiety and discomfort while preserving cooperation. The patient lies prone with a firm pillow supporting the abdomen. I do not believe that this immobilises the kidney appreciably, but it does flatten the lumbar curvature and improve access.

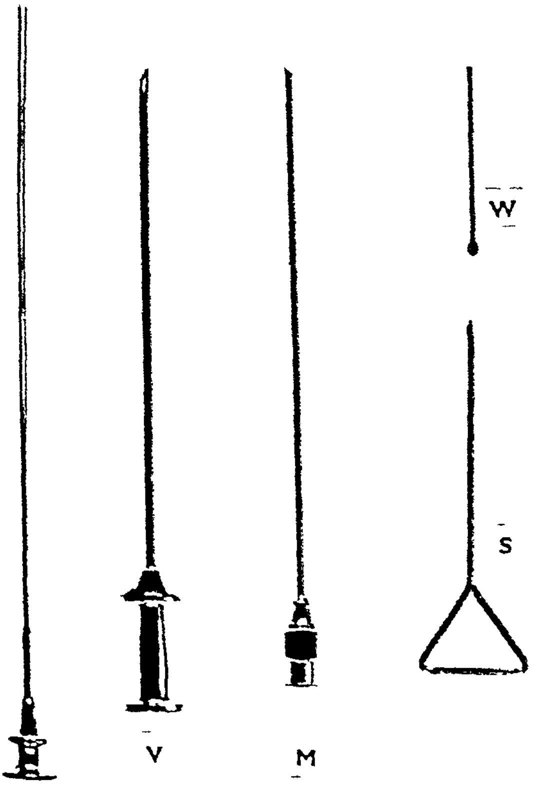

Fig 1—Menghini-type biopsy needle (M) compared with standard Vim-Silverman needle (V).

Also shown are wire stop from Menghini needle (W) and stilette used for puncturing the skin (S).

Biopsy Needle

The needle (fig 1) is a lengthened version of the liver-biopsy needle described by Menghini (1958) which I had previously found most satisfactory for its original purpose. Menghini mentioned that his needle was suitable for renal biopsy.

It has been manufactured for us in this country and is supplied with a slightly bevelled pointed end which differs from that used by Menghini for liver biopsy.* I have found that the needle performs better in vitro and in vivo if it is further sharpened with an inside bevel by means of a fine-pointed stone on a dental drill, and smoothed on an oil-stone (fig 2). The needle relies entirely on the sharpness of its edge to cut a biopsy specimen since it is not rotated during the procedure. A 10 cm needle has proved satisfactory for adults and a 7 cm needle (liver-biopsy size) for small children. We have used needles of 1·6 mm outside diameter and about 1·3 mm inside diameter which cut biopsies of about the same diameter as those obtained with the standard Franklin Vim-Silverman needle; because of its very thin walls the Menghini needle has a smaller outer diameter than the sheath of the Vim-Silverman (fig 1), and therefore makes a smaller hole in the surface of the kidney.

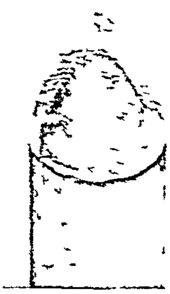

Fig 2—Enlarged view of point of Menghini biopsy needle to illustrate method of sharpening.

This needle was chosen because of its better performance in preliminary tests on isolated kidney. The Vim-Silverman needle sometimes failed in spite of transient hæmaturia which showed that the kidney had been penetrated. Various biopsy needles were therefore tested on isolated (necropsy) material under direct vision. Individual Vim-Silverman needles differed in their performance, some giving as few as 50% successful "biopsies" when inserted directly into the kidney. All Menghini needles, sharpened as described, had a "success-rate" of more than 90% when similarly tested.

Any needle for renal biopsy should be tested on isolated material before being used on patients.

Locating the Kidney

Muehrcke et al. (1955) marked on the skin the position of the kidney with the aid of a preliminary intravenous pyelogram taken with patients prone. When using their method, I compared the surface marking with the actual position of the kidney shown by a second pyelogram taken at the time of biopsy and viewed through the image-intensifier. In some patients there was considerable discrepancy—the original estimate being too low in every case. Presumably these errors are due to slight differences in the position of the patient; the phase of respiration is particularly difficult to standardise.

Considerable errors are also introduced by the magnification and distortion of the radiograph. Accuracy could be improved by meticulous standardisation of technique on all occasions, but many of the errors may be eliminated more simply by performing intravenous pyelography at the time of the biopsy.

Ten minutes after injection of the contrast medium, a wire grid is placed on the patient's back over the expected position of the lower half of the kidney from which the biopsy is to be taken. The X-ray tube is centred on the middle of this grid, and films are taken in full inspiration and full expiration. From the films, the appropriate square of the grid is chosen as the surface marking for the biopsy site, and the phase of respiration

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* The modified Menghini needle can be obtained from Charles Thackray & Co. Ltd., Park Street, Leeds.

15 sera were further tested at 37 C and found to contain hæmolysins for human A_1 cells at a titre of 1/4–1/16

These findings show that by using A^P cells, the hæmolysin test for dangerous universal donors is considerably simplified, and that a single-tube test at room temperature should result in the detection of all potentially dangerous group-O bloods 182 of the 450 sera which contained hæmolysins at 37 C hæmolysed human group-A_1 cells at room temperature, and included in these 182 sera are the 90 which contained hæmolysins at a titre of 1/8 When A^P cells are not available, a hæmolysin test at room temperature using human A_1 cells should also prove adequate, but nearly twice as many group-O bloods will then be labelled as potentially dangerous

None of the 2500 group-O bloods tested contained anti-B hæmolysins only When these were present, the sera contained anti-A hæmolysins also A test using A^P cells only is, therefore, probably sufficient, but Gardner and Tovey (1954) found 2 of 1960 *random group-O* sera with anti-B hæmolysins only In neither instance was the titre of the hæmolysin recorded, but until it has been established that anti-B hæmolysins are never present in critical titre independent of anti-A, it is a simple practical measure to use a mixture of equal volumes of a 10% suspension of pig group-A cells and human group-B cells in 1 5% saline as the test cells Of the 2500 group-O bloods tested 18 hæmolysed group-B cells at room temperature In 8 instances the anti-B hæmolysin was associated with a high-titre anti-A_1 hæmolysin, so that using a mixture of group-B human cells and A^P cells should result in fewer than 1 in 200 additional group-O bloods being labelled as " dangerous "

A further 1000 group-O sera were examined to check whether high-titre saline agglutinins and significant immune anti-A antibodies are found only in sera containing anti-A^P hæmolysins Table II shows that all of the sera containing saline anti-A agglutinins at a titre of 1/500 or immune anti-A antibodies hæmolysed the A^P cells One may conclude that a screening test for anti-A^P *hæmolysins will therefore also protect the recipient against* the transfusion of blood containing immune anti-A or saline agglutinins in high titre

TABLE II—COMPARATIVE INVESTIGATION OF 1000 SERA FOR HIGH TITRE SALINE AGGLUTININS, IMMUNE ANTI-A ANTIBODIES, AND ANTI-A^P HÆMOLYSINS

—	Titre of saline agglutinins		
	1 200	1 500	1 1000
Number showing high titre saline agglutinins	71	15	5
Number showing immune anti A	44	15	5
Number hæmolysing A^P cells	50	15	5

To determine whether complement should be added as a routine, 312 group-O sera which did not hæmolyse A_1 cells at 37 C were further tested after adding one volume of freeze-dried human complement

2 of the sera now showed hæmolysins, but only at a titre of 1 2, demonstrating that when the samples are fresh, supplementary complement is not required 15 of the sera containing anti-A^P hæmolysins were re-tested after storage at 4 C for 48 hours and 72 hours without the addition of complement All 15 stored for 48 hours hæmolysed A^P cells at room temperature, but after 72 hours storage the hæmolytic activity of 10 of the 15 sera was considerably weakened, although still detectable

It is advisable that complement should therefore be added if the hæmolysin-screening test is not carried out within 18 hours of blood-donation

Summary

A simplified test for potentially dangerous group O blood is described The test requires the incubation at room temperature of a 10% suspension of a mixture of group-A pig cells and human group-B cells, using 1 5% saline, *with an equal volume of the fresh group-O serum*

Sera containing anti-A or anti-B saline agglutinins, immune agglutinins, or hæmolysins in critically high titre, hæmolyse the test cells after incubation for 1 hour at this temperature By this technique, about 1% of group-O bloods are labelled as potentially dangerous

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RENAL BIOPSY WITH MODIFIED MENGHINI NEEDLE

DAVID N S KERR
M B , M Sc Edin , M R C P , M R C P E
FIRST ASSISTANT, THE DEPARTMENT OF MEDICINE,
UNIVERSITY OF DURHAM, NEWCASTLE UPON TYNE

IT is now nine years since acceptable methods for needle biopsy of the kidney were first introduced (Iversen and Brun 1951, Kark and Muehrcke 1954, Muehrcke et al 1955), and very few serious complications have been reported One recent series (Kark et al 1958) comprises 500 biopsies without fatality, blood-transfusion was required twice, but there were no complications requiring surgery The method used by Kark and his coworkers—biopsy in the prone position with the Franklin Vim-Silverman needle—has largely superseded the older techniques, and in the hands of its originators it gave an acceptable success-rate—80% of all attempts yielded sufficient biopsy material for diagnosis Biopsy specimens reflect the histological picture of the whole kidney in a high proportion of cases (Kellow et al 1959) Even now, however, this diagnostic aid is available in only a few British hospitals The problems that have limited its application may be appreciated from the full review of the method by Kark et al (1958), and have been underlined by personal experience and by discussion with a number of other workers in this country They are

(1) *The kidney is not an easy target*—7% of the biopsy attempts in Kark's series yielded no renal tissue, and the initial attempts of less-experienced operators (*including myself*) using their technique have had a much higher failure-rate This is doubly disturbing since *a needle which misses the kidney is in danger of hitting small bowel or colon which may be less mobile than usual owing to compression of the abdomen over* a sandbag None of Kark's patients showed unequivocal signs of bowel perforation, but this remains a real hazard to anyone who cannot locate the kidney No details are given in Kark's paper about the number of times the biopsy needle was inserted before the procedure was abandoned but some operators allow themselves two or three attempts, few could resist the temptation to explore a little deeper each time

(2) *The specimens obtained are not always histologically adequate*—The histologist is usually more interested in the cortex than in the medulla, so Kark and his colleagues used the number of glomeruli in serial section through the biopsy specimen as a criterion of adequacy Five or more glomeruli were accepted as a reasonable sample, and, on this basis, 20% of

Perinephric Infection

1 patient suffered a complication which was attributed to perinephric infection He was a child, aged 7, with severe nephrotic syndrome and moderate azotæmia due to type-I nephritis, and underwent right renal biopsy without incident Culture of the washings from the biopsy needle was sterile, but coliform organisms were found in the first midstream urine after biopsy He was given a seven-day course of sulphonamides to which the organisms were sensitive, at the same time (forty-eight hours after biopsy) prednisone therapy was begun There was no improvement in the nephrotic syndrome, but there were no complaints referable to the biopsy Two weeks later he suddenly complained of pain in the right loin, and became extremely tender there and on the right side of the abdomen His temperature rose to 100°F, and a leucocytosis of 18,000 per c mm developed over the next twenty-four hours Urine culture was sterile He was treated with erythromycin and furaltadone, and made a satisfactory recovery

Pain

Slight aching in the loin, usually at the biopsy site, and commonly related to movement, was often present in the first twenty-four hours 5 patients had more severe pain during or after biopsy 1 adult complained of loin discomfort for three days after biopsy, and another had fairly severe pain immediately after the procedure, which gradually subsided over the next four days Both were tender over the affected kidney and, although tomograms showed no evidence of large extravasation, it was thought that a small subcapsular hæmatoma might be responsible for the pain Kark et al (1958) commented that relatively small subcapsular and perinephric hæmatoma could cause quite severe discomfort

A child, with relapsing nephritis and probable Henoch's purpura, had discomfort in the loin in the first twenty-four hours after biopsy, and, five days later, a further attack of loin pain associated with slight hæmaturia In view of the time interval, the second attack may have been due to a flare-up of the illness following biopsy

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A 5th patient suffered some loin pain in association with urinary infection after biopsy

Flare-up of Original Disease

In addition to the child with nephritis 2 patients had an obvious exacerbation of their illness after biopsy A child of 14 with nephrotic syndrome was treated by bed rest and diet for one week after admission, and proteinuria fell from 15 g per litre to almost zero The day after biopsy there was no hæmaturia but urinary protein excretion rose again to 12 g per litre It fell back to zero during a course of corticotrophin (A C T H) started forty-eight hours after biopsy The specimen showed fairly severe thickening of basement membranes (type-II nephritis)

A woman of 45 with a history of recurrent loin pain and frequency had intermittently positive urinary cultures After biopsy, her urine became heavily infected with organisms similar to those in her last positive culture, and she developed typical symptoms of a urinary infection This cleared up with antibiotic therapy and she has remained well since

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Comparison of the incidence of complications in different series is of questionable value since so much depends on the observer's opinion of, for instance, where mild discomfort ends and pain begins However, the incidence of uncomfortable complications in this small series (12%) is reasonably close to that in Kark's much larger one (10%)

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A technique of renal biopsy is described which employs a modified Menghini needle and in which the position of the kidney is determined, when possible, by pyelography at the time of biopsy The results of 50 biopsy attempts are reported

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The specimens obtained by the present method contain a higher proportion of renal cortex than those taken with a Vim-Silverman needle, and are therefore more useful to the histologist

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EXPERIMENTAL STAPHYLOCOCCAL INFECTIONS IN MAN

W D Foster
M D Cantab
LECTURER IN BACTERIOLOGY, ST THOMAS'S HOSPITAL MEDICAL SCHOOL

M S R Hutt
M D Lond , M R C P
PHYSICIAN TO THE LOUIS JENNER LABORATORY, ST THOMAS'S HOSPITAL, LONDON, S E 1

THE earliest attempt to test staphylococcal virulence in man was made by Garre (1885), who rubbed an entire slope culture into the skin of his forearm This resulted in multiple pustules from which a carbuncle later developed Since this dramatic demonstration of staphylococcal virulence little experimental work has been performed in man, for obvious reasons Recently, however, Elek (1956) and Elek and Conen (1957) injected staphylococci intradermally and were able to produce small pustules with doses of over a million organisms, they were unable to produce lesions with killed cocci, and the addition of toxin did not influence the outcome

In the experiments we describe here we attempted to simulate more closely the conditions obtaining in a wound by using artificial skin lesions into which staphylococci were introduced By this method we hoped to determine whether local conditions influenced multiplication of organisms or the course of the subsequent lesion, whether different types of staphylococci varied in pathogenicity, and what was the smallest infecting dose is selected. In some patients the kidney moves several centimetres between full inspiration and full expiration, and it is therefore unwise to aim at a point close to the edge of the kidney.

All the failures and most of the complications have arisen during attempts to locate the lower pole of the kidney. Presumably this means that, even with these precautions, the surface marking of the renal outline is only approximate; attempted "biopsies" on cadavera have convinced me that the lower pole is a difficult target. Possibly one pole of the kidney can be pushed away by the biopsy needle. The site now selected for biopsy is a point about 1 inch medial to the outer edge of the kidney, between the lower and middle calyces.

Determination of the distance of the kidney from the skin has proved more difficult. After injection of local anæsthetic into the skin and lumbar muscles, a fine-bore (21 S.W.G.) exploring needle is passed vertically downwards from the surface marking until a swinging movement, related to respiration, indicates that it has entered the kidney, as described in Muehrcke's (1955) paper. The value of this sign is still uncertain, since a very similar respiratory oscillation is produced when the needle is in perinephric fat below the lower pole. This observation has been made several times with the aid of the image-intensifier. The sensation of entering the kidney substance has been noted in only about two-thirds of the patients. The most useful sign has been a pulsation, in time with the heartbeat, transmitted to the needle when it enters the kidney (Kark et al. 1958). A more certain method of determining the depth of the kidney from the surface is needed, and I am experimenting with nephrotomography at the time of biopsy as a possible alternative. Radiographs in two planes were utilised by Iversen and Brun (1951), but the distance of the kidney from the lateral film makes accurate measurement difficult.

Aspiration of Biopsy

The needle is used as in liver biopsy (Menghini 1958). A tiny incision is made in the skin and the needle, attached to a syringe, is inserted to a depth of about 1 cm. A few drops of saline are blown through the needle to clear it of fat, &c., and it is then inserted into the kidney and withdrawn in one rapid movement, with suction applied to the syringe throughout. Suction must be maintained during insertion of the needle, and this requires a little practice which is best obtained on the cadaver. Either a guard, as fitted to a sternal puncture needle, or the finger, can be used, to prevent too deep insertion of the biopsy needle. The specimen remains in the needle, and is blown out into preservative. If no biopsy is obtained, a second insertion of the needle is permissible, and has been required in about one-third of the biopsy attempts.

Results

This procedure has been tried 50 times, and 48 specimens of renal tissue have been obtained. The specimens were handled by the routine histological laboratory, and counts of the number of glomeruli in a single section through each specimen have been taken from the original slides. The results are shown in the table, and are compared with figures derived from fig. 2 in the article by Kark et al. (1958). Where several sections were cut for different stains, the highest individual count is quoted. Better results could be obtained by careful sectioning along the centre of the biopsy specimen and by serial sectioning, but these have not been carried out routinely.

NUMBER OF GLOMERULI IN SINGLE SECTIONS THROUGH BIOPSY SPECIMENS

Number of glomeruli per section	Number of specimens in this group	Percentage of all attempts	Corresponding percentage in series of Kark et al. (1958)
0 (a) No renal tissue	2	4	7
0 (b) Renal tissue but no glomeruli	0	0	5
1–4	2	4	15
5–9	6	12	30
10–14	8	16	22
15–19	8	16	8
20–24	14	28	7
Over 24	10	20	5
5 or more	46	92	73
10 or more	40	80	42

Kark's criterion of adequacy cannot therefore be applied to the present material, but, using a stricter requirement of five glomeruli per single section, an acceptable biopsy was obtained in 46 of 50 attempts (92%). The average number of glomeruli per slide was twenty-one, which is about twice the figure for Kark's series, suggesting that specimens taken by the new technique contain more renal cortex.

There is no simple measure of the amount of renal medulla on a slide, and Kark et al. gave no indication of the amount in their specimens. Using a rough rule-of-thumb classification of "adequate" or "inadequate", it was estimated that 11 specimens contained too little medulla; my impression is that a higher proportion of biopsies taken with the Vim-Silverman needle contain adequate medulla, but there is insufficient material for a fair comparison. In any case, present histological opinion appears to be that in making a diagnosis the amount of cortex is much more important than the amount of medulla.

In 12 of the patients, a high blood-urea precluded the use of pyelography to locate the kidney. Plain films or tomograms of the renal area were taken to ensure that two kidneys were present in roughly the normal position. The biopsy needle was inserted vertically downwards about 1 cm. below the last palpable right rib, 6–7 cm. from the midline. A specimen was obtained without difficulty in 11 cases, and, in the 12th, a specimen was obtained on a third insertion of the needle immediately below the twelfth rib. Diagnosis was important in this patient, and the making of several attempts was thought justifiable. Although the success-rate in the "blind-biopsy" group is therefore as high as in the remainder of the series, I am convinced that radiographic localisation should be employed whenever possible.

5 children, aged 8–14, have undergone successful renal biopsy under local anæsthesia. In one child, aged 7, the procedure was carried out under brief general anæsthesia.

Complications

The main complications described by other workers are hæmorrhage (hæmaturia and perinephric hæmatoma), perinephric infection, pain (loin pain and renal colic), flare-up of previous illness (particularly renal infection), and biopsy of the wrong organ.

Hæmorrhage

There was visible hæmaturia (usually slight) in the first one or two urine specimens passed after biopsy in about half of the patients, and microscopic hæmaturia was found in the remainder whenever it was looked for. No patient developed gross or prolonged hæmaturia, or significant fall in hæmoglobin level, after biopsy, and no transfusions were required. Perinephric hæmorrhage is more difficult to detect, but a large hæmatoma [illegible] to produce a shadow on [illegible] Nephrotomograms [illegible] of the renal area (Kark et al. 1958). Plain films were taken in every patient who had significant pain after biopsy, and tomograms were taken in 2; no hæmatoma was detected.

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The earliest attempt to test staphylococcal virulence in man was made by Garre (1885), who rubbed an entire slope culture into the skin of his forearm This resulted in multiple pustules from which a carbuncle later developed Since this dramatic demonstration of staphylococcal virulence little experimental work has been performed in man, for obvious reasons Recently, however, Elek (1956) and Elek and Conen (1957) injected staphylococci intradermally and were able to produce small pustules with doses of over a million organisms, they were unable to produce lesions with killed cocci, and the addition of toxin did not influence the outcome

In the experiments we describe here we attempted to simulate more closely the conditions obtaining in a wound by using artificial skin lesions into which staphylococci were introduced By this method we hoped to determine whether local conditions influenced multiplication of organisms or the course of the subsequent lesion, whether different types of staphylococci varied in pathogenicity, and what was the smallest infecting dose

TABLE I—PHAGE TYPE AND SOURCE OF *Staph. aureus* USED IN EXPERIMENTS

Phage type	Source
n t	Perineal carrier
n t	Nasal carrier
47/77	" "
52/80	" "
3c/55/71*	Septic wound

n t = not typable with the routine set of phage

* = this organism was obtained from an outbreak of wound sepsis (Foster 1960)

Materials and Methods

The strains of staphylococci were isolated on blood-agar and identified by their colonial appearance and slide-coagulase tests The strains were stored on agar slopes in bijou bottles, and then phage-typed by the method of Anderson and Williams (1956) The phage-type and origin of the various organisms used in these experiments are listed in table I All were coagulase-positive *Staphylococcus aureus* (with the exception of a coagulase-negative *Staph. albus* used in one experiment), and all were sensitive to the standard antibiotics

The experimental lesions were made by scraping the epithelium from a small area of skin on the volar surface of the forearm (Rebuck and Yates 1954) Using a scalpel with a small blade, twenty-five strokes were made, this manœuvre resulting in a lesion of constant size which did not bleed, but in the base of which capillary loops were easily visible The lesions produced in this way were inoculated with a standard platinum loop delivering about 0·005 ml of an overnight 'Lemco' broth culture containing about 250 × 10^6 organisms per ml The standard inoculum was thus approximately 10^6 organisms The lesions were then sealed with circular flamed coverslips which were held in position with 'Sellotape'

TABLE II—COMPARISON OF THE MULTIPLICATION OF ORGANISMS IN STANDARD SKIN LESIONS SEALED WITH COVERSLIPS AND LEFT EXPOSED

Time after inoculation	No of organisms recovered	
	Lesions sealed with coverslips	Lesions allowed to dry
15 min	0·7 × 10^6	0·7 × 10^6
2 hours	1·8 × 10^6	0·5 × 10^6
5 "		0·4 × 10^6
8 "	18 × 10^6	0·8 × 10^6
17 "	25 × 10^6	
27 "	55 × 10^6	2·6 × 10^6

Staphylococcal Counts from Skin Lesions

The coverslip and sellotape over each lesion were stripped off and dropped into 10 ml of nutrient broth in a wide-mouth universal container One drop of sterile broth was then added to the underlying lesion, and the whole area was thoroughly rubbed with two sterile alginate wool swabs to remove all exudate and superficial layers of the lesion Both swabs were then broken off into the same sample of nutrient broth as the coverslip After capping, the universal container was shaken vigorously until the alginate swabs disintegrated

Serial tenfold dilutions were then prepared in broth using [illegible] ml dropping pipettes, and each dilution was plated out After overnight incubation the colonies of staphylococci were counted, and from these counts the number recovered from the whole lesion was calculated In experiments in which coverslips were not used to seal the lesions organism counts were obtained by firm swabbing of the area with alginate swabs after preliminary moistening with broth The swabs were then dropped into the universal containers as before

Results

Multiplication of Organisms

Five standard skin lesions were made in two subjects and inoculated as described above with phage-type 3c/55/71 In one subject the lesions were covered with coverslips and in the other they were left exposed Counts were then made of the numbers of organisms obtained at various times after inoculation

It will be seen from table II that the covered lesions showed considerable increase in the numbers of organisms between 2 and 8 hours, followed by a slower increase over the next 14 hours, whereas there was virtually no increase in numbers in the uncovered lesions even after 24 hours Macroscopically, the covered lesions showed a purulent exudate after a few hours in contrast to the uncovered lesions, which formed a scab with scanty exudate

Effect of Foreign Material

In view of the possibility that foreign material might influence the results, the effect of rubbing starch and french chalk into the lesions was investigated

Six standard skin lesions were made and treated as indicated in table III They were then covered with the lids of small bijou bottles which were strapped on to the arm, keeping the lesions moist but avoiding the direct pressure inevitable with a coverslip The lesions were left for 24 hours, after which they were inspected and organism-counts were made

TABLE III—COMPARISON OF ORGANISM COUNTS AND MACROSCOPIC APPEARANCES IN LESIONS TREATED WITH FOREIGN MATERIAL

Lesion	Appearance at 24 hours	Organism count at 24 hours	Appearance at 48 hours
1 Control	Serous exudate	0	No erythema
2 Standard loopful of staphs	Purulent exudate	19 × 10^6	Erythema +
3 Standard loopful of staphs + french chalk	" "	17 × 10^6	"
4 French chalk	Dry lesion	0	No erythema
5 Staphs + starch	Purulent exudate	13 × 10^6	Erythema +
6 Starch	Slight serous exudate	0	No erythema

The results show no apparent macroscopic difference between the lesions produced in this series and those in which coverslips had been used, although the rate of multiplication of organisms was slower with the bijou-cap method There was also no significant difference between the lesions to which foreign material had been added and those which were uncontaminated

Inflammatory Responses in Skin Lesions Infected by Staphylococci

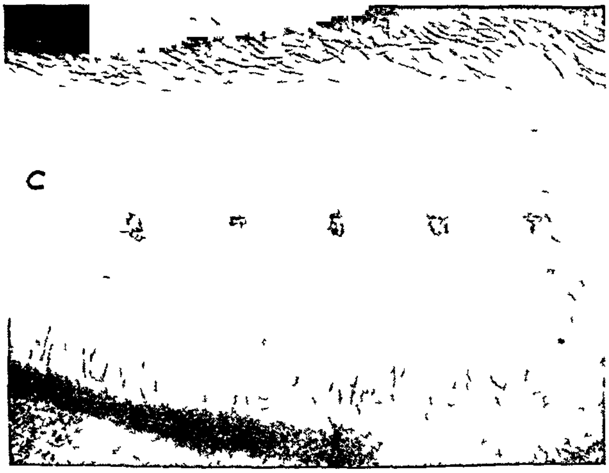
Three skin lesions were made, one of which acted as a control, while the other two were inoculated with a standard loopful of a 24-hour culture of *Staph. albus* or *Staph. aureus* (phage-type 3c/55/71) respectively (table IV) The lesions were then sealed with coverslips, which were changed at intervals during the next 24 hours The cellular exudate on these coverslips was stained by methylene-blue and examined microscopically The state of the lesion was recorded after 24 hours

The essential cytological difference between the infected and the control lesions was the increasing numbers of degenerate polymorphonuclear leucocytes in the infected lesions, whereas

TABLE IV—COMPARISON OF THE INFLAMMATORY RESPONSES IN SKIN LESIONS INFECTED BY *Staph. albus* AND *Staph. aureus*

Time of application of coverslips	Cytology	Control (uninoculated)	*Staph. albus*	*Staph. aureus*
5–8 hours	Polymorphs	++	++	++
	Degenerate polymorphs	+	+	+++
	Mononuclears	++	++	+
	Staphylococci	–	+	++
9–13 hours	Polymorphs	++	++	+
	Degenerate polymorphs	+	++	+++
	Mononuclears	+++	++	+
	Staphylococci	–	+	+
13–24 hours	Polymorphs	++	++	+
	Degenerate polymorphs	+	+++	++++
	Mononuclears	+		+
	Staphylococci	–	++	+
Macroscopic appearance at 24 hours [illegible]		Serous exudate no erythema	Seropurulent exudate slight erythema	Purulent exudate [illegible] erythema

[illegible]



Comparison of the control skin lesion, C, and lesions inoculated with five different types of *Staph aureus*

in the control lesion mononuclear and histiocytic cells increased for 13 hours, when they dominated the picture Although phagocytosis of organisms by polymorphs was seen on all the coverslips from the infected lesions most organisms were extracellular

Different Types of aureus and Their Inflammatory Responses

Six standard skin lesions were made, five of these were inoculated with the five different types of *Staph aureus* listed in table I The lesions were then sealed with coverslips which were changed at intervals, as already described After 24 hours all the inoculated lesions showed surrounding erythema and were covered with a purulent exudate, whereas the uninoculated lesion was not erythematous and showed only slight exudate (see figure) There was no essential difference between the lesions produced by the different types of organisms

Organism Dose and Inflammatory Response

Two sets of five standard lesions were made and inoculated with dilutions of a 24-hour broth culture of *Staph aureus* (phage-type 3c/55/71) Four of the lesions of one of these sets were inoculated with 100, 1000, 10,000, and 1,000,000 organisms respectively, while the other set was seeded with 240, 120, 60, 30, and 15 organisms In each set the fifth lesion was inoculated with broth as a control

The results of the larger dose inoculum are shown in table V There was little difference between lesions 2, 3, and 4 although the exudate was increased slightly with increasing numbers of organisms Lesion 5, however, by contrast showed a frankly purulent exudate, and it was indurated and sore After removal of the coverslips all these lesions dried up and were healed within a week

The results of the smaller dose inoculum, shown in table VI, indicate that as few as fifteen organisms are sufficient to cause a septic lesion, and they illustrate the rapidity with which the organisms can multiply

The Staphylococcal Lesions

In the course of these experiments, two of the three subjects developed skin lesions of some severity on the inoculated arm Soon after inoculation one got a boil and a crop of small pustules in the hairy part of the arm and over the sites of a sellotape reaction, 5 weeks after his last inoculation he developed a further boil in the same area The organisms from these lesions all belonged to phage-type 3c/55/71 The other subject, who also had some boils on the arm immediately after inoculation, got a large boil on the thigh as well 2 weeks after the last inoculation of organisms This subject, who had never previously been a nasal carrier of *Staph aureus*, was at that time found to be carrying phage-type 3c/55/71 in his nose The boil on his thigh resolved with local treatment, and the nasal carriage was cleared up with a cream containing chlorhexidine and neomycin (' Naseptin ') But 2 weeks later a large abscess developed on the buttock, from which was again grown phage-type 3c/55/71 Before this abscess appeared he had not been a perineal carrier of *Staph aureus*

TABLE V—COMPARISON OF ORGANISM-COUNTS AND MACROSCOPIC APPEARANCES OF LESIONS TREATED WITH DIFFERENT DOSES OF *Staph aureus*

Lesion	Appearance at 24 hours	Organism-count at 24 hours
1 Control	No exudate, no erythema	0
2 100 organisms	Seropurulent exudate erythema 5 × 5 mm	$5\ 2 \times 10^6$
3 1000 "	Seropurulent exudate erythema 7 × 7 mm	$8\ 0 \times 10^6$
4 10 000 "	Seropurulent exudate erythema 7 × 7 mm	$11\ 0 \times 10^6$
5 1 000 000 "	Purulent exudate, erythema 15 × 15 mm	$21\ 0 \times 10^6$

Discussion

Despite the extensive reports which have accumulated on the epidemiology of staphylococcal infections, the factors which determine the development of septic lesions in any person remain largely unsolved Although clinical evidence suggests that certain phage-types of staphylococci are more virulent than others (Barber and Burston 1955), and that passage through a septic lesion also enhances virulence (Beavan and Burry 1956), there is no direct experimental evidence that different strains of *Staph aureus* differ in virulence Elek (1956) and Elek and Conen (1957) attempted to test the behaviour of staphylococci in man by injecting them intradermally They produced small septic lesions with 1–5 million organisms, but were unable to demonstrate any difference in the smallest pus-forming dose between strains obtained from lesions or from healthy nasal carriers and epidemic strains

TABLE VI—DETERMINATION OF THE SMALLEST INFECTING DOSE

Organisms applied	Organisms recovered at 24 hours	Macroscopic appearances at 24 hours
240	$18\ 5 \times 10^6$	Seropurulent exudate with erythema
120	$10\ 5 \times 10^6$	
60	$11\ 5 \times 10^6$	
30	$11\ 0 \times 10^6$	
15	$6\ 1 \times 10^6$	
0 (broth only)	0	

Using a similar organism dose we have shown that it is possible to demonstrate differences in skin reaction between an uninfected lesion, one inoculated with *Staph aureus*, and one inoculated with *Staph albus* The *Staph albus* lesion was clearly infected in contrast to the control but the inflammatory reaction was less than in the lesion infected by *Staph aureus*

In a similar experiment four types of *Staph aureus* which had not been associated with infections were compared with a strain (phage-type 3c/55/71) known to have caused several infections It was not possible to differentiate between the macroscopic or microscopic features of these five lesions at the end of 24 hours all showed a similar purulent exudate with surrounding erythema These results confirm those of Elek and Conen (1957), who also attempted to differentiate between lesions produced by organisms from carriers, and those from septic lesions, without success

The multiplication of staphylococci in these standard infected lesions covered with coverslips followed the expected pattern of growth, with a lag phase followed by a phase of rapid multiplication But in similar experiments in which the lesions remained uncovered after inoculation, multiplication was delayed for 8 hours It seems probable that keeping the lesion moist was the significant factor since the 24-hour count after a standard inoculation was similar whether the lesions were covered with coverslips, or with small lids which retained moisture without causing pressure on the lesion No evidence was forthcoming that the application of foreign material, such as french chalk or starch, which are used in glove powders, influenced the multiplication of organisms or the 24 hours' inflammatory response Superficial foreign material, however, cannot be compared with deep foreign bodies, such as sutures The experimental work of Elek and Conen (1957) has shown that sutures have a significant effect in determining a clinical lesion

In all the initial experiments in our study the organism numbers in the inoculum were mostly of an order similar to those used by Elek (1956), and thus they bore little relation to clinical reality In our dilution experiments, however, we found that as few as fifteen organisms could still produce significant sepsis in a standard skin lesion, and also that multiplication of organisms was so rapid that the total organism count at 24 hours was not much different from those infected with larger inocula In so far as these experimental skin lesions simulated operation wounds, the results indicate that wound infection could also develop after initial contamination with small numbers of organisms The significance of this finding is enhanced by the observation of Foster (1960), who demonstrated the deposition of occasional staphylococci on an artificial operation site by a carrier using full aseptic technique

The unplanned subsequent septic lesions in two experimental subjects curtailed further experiments, but illustrated some additional aspects of the behaviour of *Staph aureus* in the body The boils on the arms were not necessarily at the site of inoculation but were always centred on hair follicles These findings are in line with clinical experience and with the experimental work of Bockhart (1887), who excised experimentally produced furuncles and showed histologically that the organisms had multiplied in hair follicles It may be of significance in this connection that of the three subjects of this experiment the one who escaped infection entirely was a woman, and the one most severely affected was the most hirsute This subject, who later became a nasal carrier and developed abscesses on the thigh and buttock, illustrates the propensity of the *Staph aureus* to spread all over the body from an initial infective site, and the importance of separating such infected individuals from the neighbourhood of uninfected healing wounds

Summary

Artificial skin lesions produced in man were inoculated with staphylococci Organisms multiplied rapidly if the lesions were kept covered There was a difference between the inflammatory response produced by *Staphylococcus albus* and *Staph aureus*, but no evidence that different types of *Staph aureus* varied in their virulence

The addition of superficial foreign material did not affect the eventual lesion Multiplication of organisms with the production of a septic lesion could be produced by as few as fifteen organisms

The experiments had to be terminated because of the development of other septic lesions in two of the subjects

Our thanks are due to Dr E H [illegible] who volunteered to take part in one experiment and to Prof Ronald Hare for helpful criticism

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"BURNING LIPS" ASSOCIATED WITH ŒSOPHAGEAL REFLUX

MAURICE GARRETTS
M B Lond , M R C P
SENIOR REGISTRAR, DEPARTMENT OF DERMATOLOGY, UNIVERSITY
COLLEGE HOSPITAL LONDON, W C 1

BECAUSE of the unusual presentation, three cases in which œsophageal reflux was shown radiographically are reported

Case-records

Case 1 —A man, aged 60, employed in a wallpaper factory, complained that for the previous two years he had been constantly troubled by a burning sensation of the tongue, lips, and inside of the mouth generally, this had been worse for the past nine months He had had colitis, but the last attack was five years ago He admitted that for many years he had "brought up a lot of wind", especially after meals He said that he could taste food long after a meal had been taken, and that he had a foul taste in his mouth for most of the day

The lips appeared normal The whole of the buccal mucosa was reddened, but the reddening was less intense over the surface of the hard palate under the upper dental plate

The patient was sure that his dentures had nothing to do with the condition since it had failed to improve when he left them out for several weeks Patch tests, using denture materials, were negative Hydrocortisone preparations applied locally to the buccal mucosa, sedatives, and injections of 'Parentrovite' had no effect on the condition He was not anæmic Because he worked in a wallpaper factory, his urine was examined for excessive amounts of arsenic, which, however, were not found

Despite the absence of pain in the chest or the abdomen, the acid taste in his mouth, together with eructations of copious wind, might have been due to a lesion of his œsophagus A barium swallow showed a sliding hiatus hernia There was free reflux Some coarsening of the mucosal folds, compatible with œsophagitis, was seen in the lower œsophagus No abnormality was demonstrated radiographically in the stomach or duodenum

He was advised to sleep propped well up on pillows to reduce nocturnal reflux, and to take 'Nulacin' tablets regularly, but, despite several months of medical treatment, the symptoms have persisted Œsophagoscopic examination is to be made, and, if necessary, the hiatus hernia will be treated surgically

Case 2.—A man, aged 52, complained of recurrent swellings of the lower lip, together with a burning sensation, and sometimes blistering and superficial ulceration of the lower lip for the past seven months He said he had a most "foul and disgusting" taste in his mouth, particularly in the mornings For many years he often had to rise at night and wash out his mouth because of the "dreadful acid taste"

No blistering was seen, but there was some superficial denudation, resembling aphthæ, of the buccal surface of the *lower lip* There was no erythema of the buccal mucosa, which was perfectly normal in all other areas Leaving his dentures out for six weeks had no effect There was no association with any particular food or drink Just before the onset of the condition, he had fallen down stairs, and, after this accident, *he had a pain in his neck Because of this pain,* he was unable to tolerate his usual number of pillows in bed, and had developed the habit of lying flat

Barium meal showed that there was no hiatus hernia, but with the patient in the Trendelenburg position, barium was regurgitated into the lower œsophagus

In this case the recently acquired habit of sleeping flat seems to have been responsible for the onset of the burning sensation and for the superficial ulceration of the lower lip He was advised to raise the head of his bed on blocks

Case 3 —A woman, aged 65, complained of a [illegible] taste in the mouth for the past [illegible] months She also complained [illegible] her [illegible] the lips [illegible] small painful [illegible] mucosa She had nocturnal indigestion which was relieved by sitting up in bed

A barium meal elsewhere showed no abnormality No amalgam was present in her teeth, and her dentures contained no metal She was not anæmic

A barium meal showed some regurgitation of barium into the lower œsophagus when the patient was supine, but a definite hiatus hernia could not be demonstrated

Discussion

All the patients complained of burning sensations of the buccal mucosa, and, except for case 3, they were free from any abdominal pain or indigestion They all were shown to produce œsophageal reflux in the supine position

While aphthosis affecting mucous membranes other than in the mouth must be regarded in a different light, recurrent ulceration of the buccal mucosa, with painful erosions, might profitably be reviewed in the light of this experience It may be that these lesions, and perhaps those called "dyspeptic ulcers" of the mouth, may in fact be due to the action of gastric secretions on the buccal mucosa

Summary

Three cases are reported in which the patients complained of burning sensations of the tongue, lips, and buccal mucosa, and of an unpleasant taste in the mouth Two of them had patches of mucosal erosion, resembling aphthous ulceration

In all three, when supine, stomach contents were shown radiographically to be regurgitated One patient had a sliding hiatus hernia, but no such abnormality was found in the others

Œsophageal reflux is suggested as a possible cause of some so-called " dyspeptic ulcers " of the mouth

I should like to thank Dr P J Hare and Prof R S Pilcher for permission to publish these cases, and I am most grateful to Dr K M Harvey for drawing my attention to case 3

THE TREATMENT OF DRUG-ADDICTION

I M Frankau
M D Lond

Patricia M Stanwell
M R C S

In September, 1957, we began to treat three young patients who had become addicted to drugs at an early age and who had never made satisfactory adjustment to life They professed themselves anxious to be cured, but two had already been deprived of drugs for a short time while serving a prison sentence for obtaining drugs illegally, and both readily admitted that while in prison they thought always of when they would be free and could go back to drugs

We decided to withdraw the drugs as quickly as possible, to give intensive psychiatric treatment while the patients were in the nursing-home, and to follow this by finding them suitable employment in a new environment But unfortunately we had underestimated the skill and tenacity of the drug pedlars and their associates

Each of these patients left the nursing-home without withdrawal symptoms, in a reasonable state of health, and determined to keep clear of drugs But within a fortnight all three were taking drugs again, and were once more under the control of the pedlars The method of treatment which had proved successful in alcoholic patients—firstly detoxication and the creation of a sense of wellbeing, and secondly intensive psychotherapy and vitamin therapy—was evidently useless for these drug addicts It was obvious that before withdrawal there must be a preliminary period during which the patients were adequately prepared, both psychologically and physiologically, for complete withdrawal of the drugs of addiction

If the patient was to make a successful effort to face life without drugs, especially when crises arise, there must be a strong enough incentive to seek treatment, and sufficient insight to realise that personal difficulties are a major factor in the illness A negative attitude—e g , asking for help because of difficulties with the authorities, or domestic or financial problems—was only effective for a comparatively short time It was also essential that the patient should realise clearly that withdrawal of drugs alone would not free him from a recurrence of craving for the effects of the drug

The Series

We have excluded from our later series patients from whom we did not obtain a life-history which could be verified, and also those who were addicted to barbiturates and tranquillisers The remaining fifty-one patients were treated between August, 1958, and March, 1960 The earlier ones were referred to I M F from P M S's general practice, most of the others were advised to seek treatment by patients already treated They fell into 3 main groups

Group 1

Nine patients, aged 28–47, for adequate medical reasons, had been given narcotic drugs—morphine, 'Omnopon', or pethidine—and had continued to obtain a supply of the drug, legally or illegally, after the original need had passed All probably had a low threshold for pain and discomfort, and they had developed a low threshold for anxiety, detailed analyses revealed underlying personality difficulties None of these patients used diamorphine (heroin) or cocaine, and only one resorted to forging prescriptions in order to obtain pethidine Drugs were obtained either wholly or partially from a medical practitioner, extra supplies being acquired illegally

Group 2

Six patients, aged 45–55, came from the higher social and economic levels, and had relatively high intellectual achievements They had taken drugs originally " in order to live more fully ", and three of them had lived reasonably useful lives for over 20 years after becoming addicted

Those receiving medical prescriptions for their entire supply of drugs were able to maintain a reasonable social and economic level, but those buying from pedlars to supplement supplies went steadily downhill and eventually were unable to provide regular food and adequate lodging The energy and concentration which should have been devoted to making a success of a profession or business were directed to the pursuit of drugs, which alone could give relaxation, a sense of security, and freedom from anxiety All six patients had taken both heroin and cocaine

Group 3

The largest group of thirty-six patients had many characteristics in common despite individual differences Their ages ranged from 18 to 32 years Behind most were broken homes, unhappy parental relationships, lack of discipline or (less often) too rigid discipline, and either lack of security or over-indulgence by one or both parents, which had resulted in inability to adapt to the normal hazards of life

These patients were immature, inadequate, and unstable, they had failed to develop normal relationships with family and friends, and lacked willpower or any form of self-discipline They had a low threshold for pain and discomfort, were unable to tolerate criticism, and equally unable to bear frustration They lived for the immediate gratification of their desire for drugs, and were totally without concern for the welfare of or with small lids which retained moisture without causing pressure on the lesion No evidence was forthcoming that the application of foreign material, such as french chalk or starch, which are used in glove powders, influenced the multiplication of organisms or the 24 hours' inflammatory response Superficial foreign material, however, cannot be compared with deep foreign bodies, such as sutures The experimental work of Elek and Conen (1957) has shown that sutures have a significant effect in determining a clinical lesion

In all the initial experiments in our study the organism numbers in the inoculum were mostly of an order similar to those used by Elek (1956), and thus they bore little relation to clinical reality In our dilution experiments, however, we found that as few as fifteen organisms could still produce significant sepsis in a standard skin lesion, and also that multiplication of organisms was so rapid that the total organism count at 24 hours was not much different from those infected with larger inocula In so far as these experimental skin lesions simulated operation wounds, the results indicate that wound infection could also develop after initial contamination with small numbers of organisms The significance of this finding is enhanced by the observation of Foster (1960), who demonstrated the deposition of occasional staphylococci on an artificial operation site by a carrier using full aseptic technique

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"BURNING LIPS" ASSOCIATED WITH ŒSOPHAGEAL REFLUX

Maurice Garretts
M B Lond, M R C P
SENIOR REGISTRAR, DEPARTMENT OF DERMATOLOGY, UNIVERSITY COLLEGE HOSPITAL, LONDON, W C 1

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The lips appeared normal The whole of the buccal mucosa was reddened, but the reddening was less intense over the surface of the hard palate under the upper dental plate

The patient was sure that his dentures had nothing to do with the condition since it had failed to improve when he left them out for several weeks Patch tests, using denture materials, were negative Hydrocortisone preparations applied locally to the buccal mucosa, sedatives, and injections of 'Parentrovite' had no effect on the condition He was not anæmic Because he worked in a wallpaper factory, his urine was examined for excessive amounts of arsenic, which, however, were not found

Despite the absence of pain in the chest or the abdomen, the acid taste in his mouth, together with eructations of copious wind, might have been due to a lesion of his œsophagus A barium swallow showed a sliding hiatus hernia There was free reflux Some coarsening of the mucosal folds, compatible with œsophagitis, was seen in the lower œsophagus No abnormality was demonstrated radiographically in the stomach or duodenum

He was advised to sleep propped well up on pillows to reduce nocturnal reflux, and to take 'Nulacin' tablets regularly, but, despite several months of medical treatment, the symptoms have persisted Œsophagoscopic examination is to be made, and, if necessary, the hiatus hernia will be treated surgically

Case 2 —A man, aged 52, complained of recurrent swellings of the lower lip, together with a burning sensation, and sometimes blistering and superficial ulceration of the lower lip for the past seven months He said he had a most " foul and disgusting " taste in his mouth, particularly in the mornings For many years he often had to rise at night and wash out his mouth because of the " dreadful acid taste "

No blistering was seen, but there was some superficial denudation, resembling aphthæ, of the buccal surface of the lower lip There was no erythema of the buccal mucosa, which was perfectly normal in all other areas Leaving his dentures out for six weeks had no effect There was no association with any particular food or drink Just before the onset of the condition, he had fallen down stairs, and, after this accident, he had a pain in his neck Because of this pain, he was unable to tolerate his usual number of pillows in bed, and had developed the habit of lying flat

Barium meal showed that there was no hiatus hernia, but, with the patient in the Trendelenburg position, barium was regurgitated into the lower œsophagus

In this case the newly acquired habit of sleeping flat seems to have been responsible for the onset of the burning sensation and for the superficial ulceration of the lower lip He was advised to raise the head of his bed on blocks

Case 3 —A woman, aged 65, complained of a metallic taste in the mouth for the past six months She also complained that her tongue was sore, and that she was troubled by soreness of the lips associated with small painful erosions on the buccal mucosa. She had nocturnal indigestion which was relieved by sitting up in bed

A barium meal elsewhere showed no abnormality No amalgam was present in her teeth, and her dentures contained no metal She was not anæmic

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Discussion

All the patients complained of burning sensations of the buccal mucosa, and, except for case 3, they were free from any abdominal pain or indigestion They all were shown to produce œsophageal reflux in the supine position

While aphthosis affecting mucous membranes other than in the mouth must be regarded in a different light, recurrent ulceration of the buccal mucosa, with painful erosions, might profitably be reviewed in the light of this experience It may be that these lesions, and perhaps those called "dyspeptic ulcers" of the mouth, may in fact be due to the action of gastric secretions on the buccal mucosa

Summary

Three cases are reported in which the patients complained of burning sensations of the tongue, lips, and buccal mucosa, and of an unpleasant taste in the mouth Two of them had patches of mucosal erosion, resembling aphthous ulceration

In all three, when supine, stomach contents were shown radiographically to be regurgitated One patient had a sliding hiatus hernia, but no such abnormality was found in the others

Œsophageal reflux is suggested as a possible cause of some so-called " dyspeptic ulcers " of the mouth.

I should like to thank Dr P J Hare and Prof R S Pilcher for permission to publish these cases, and I am most grateful to Dr K M Harvey for drawing my attention to case 3

THE TREATMENT OF DRUG-ADDICTION

I M FRANKAU
M.D Lond

PATRICIA M STANWELL
M R C S

IN September, 1957, we began to treat three young patients who had become addicted to drugs at an early age and who had never made satisfactory adjustment to life They professed themselves anxious to be cured, but two had already been deprived of drugs for a short time while serving a prison sentence for obtaining drugs illegally, and both readily admitted that while in prison they thought always of when they would be free and could go back to drugs

We decided to withdraw the drugs as quickly as possible, to give intensive psychiatric treatment while the patients were in the nursing-home, and to follow this by finding them suitable employment in a new environment But unfortunately we had underestimated the skill and tenacity of the drug pedlars and their associates

Each of these patients left the nursing-home without withdrawal symptoms, in a reasonable state of health, and determined to keep clear of drugs But within a fortnight all three were taking drugs again, and were once more under the control of the pedlars The method of treatment which had proved successful in alcoholic patients—firstly detoxication and the creation of a sense of wellbeing, and secondly intensive psychotherapy and vitamin therapy—was evidently useless for these drug addicts It was obvious that before withdrawal there must be a preliminary period during which the patients were adequately prepared, both psychologically and physiologically, for complete withdrawal of the drugs of addiction

If the patient was to make a successful effort to face life without drugs, especially when crises arise, there must be a strong enough incentive to seek treatment, and sufficient insight to realise that personal difficulties are a major factor in the illness A negative attitude—e g , asking for help because of difficulties with the authorities, or domestic or financial problems—was only effective for a comparatively short time It was also essential that the patient should realise clearly that withdrawal of drugs alone would not free him from a recurrence of craving for the effects of the drug

The Series

We have excluded from our later series patients from whom we did not obtain a life-history which could be verified, and also those who were addicted to barbiturates and tranquillisers The remaining fifty-one patients were treated between August, 1958, and March, 1960 The earlier ones were referred to I M F from P M S's general practice, most of the others were advised to seek treatment by patients already treated They fell into 3 main groups

Group 1

Nine patients, aged 28–47, for adequate medical reasons, had been given narcotic drugs—morphine, 'Omnopon', or pethidine—and had continued to obtain a supply of the drug, legally or illegally, after the original need had passed All probably had a low threshold for pain and discomfort, and they had developed a low threshold for anxiety, detailed analyses revealed underlying personality difficulties None of these patients used diamorphine (heroin) or cocaine, and only one resorted to forging prescriptions in order to obtain pethidine Drugs were obtained either wholly or partially from a medical practitioner, extra supplies being acquired illegally

Group 2

Six patients, aged 45–55, came from the higher social and economic levels, and had relatively high intellectual achievements They had taken drugs originally " in order to live more fully ", and three of them had lived reasonably useful lives for over 20 years after becoming addicted

Those receiving medical prescriptions for their entire supply of drugs were able to maintain a reasonable social and economic level, but those buying from pedlars to supplement supplies went steadily downhill and eventually were unable to provide regular food and adequate lodging The energy and concentration which should have been devoted to making a success of a profession or business were directed to the pursuit of drugs, which alone could give relaxation, a sense of security, and freedom from anxiety All six patients had taken both heroin and cocaine

Group 3

The largest group of thirty-six patients had many characteristics in common despite individual differences Their ages ranged from 18 to 32 years Behind most were broken homes, unhappy parental relationships, lack of discipline or (less often) too rigid discipline, and either lack of security or over-indulgence by one or both parents, which had resulted in inability to adapt to the normal hazards of life

These patients were immature, inadequate, and unstable, they had failed to develop normal relationships with family and friends, and lacked willpower or any form of self-discipline They had a low threshold for pain and discomfort, were unable to tolerate criticism, and equally unable to bear frustration They lived for the immediate gratification of their desire for drugs, and were totally without concern for the welfare of others Any crisis or difficulty was followed by urgent demands for an increased supply of drugs

They avoided responsibility, lacked normal healthy interests and ambitions, and generally failed to keep a job for any length of time With the increasing loss of power to control the need for frequent intravenous injections they became more unstable and more anxious, and consequently increasingly dependent on drugs for relief of tension Some seemed capable of maintaining reasonable ethical and moral standards apart from anything connected with the drug About things even remotely concerned with their drugs they were untruthful and unreliable, making less and less effort to appear plausible

Among themselves they had a rigid code They would not inform about associates from whom they borrowed or bought drugs, or to whom they lent or sold They were incapable of reasonable ethical judgment about the activities of the pedlars, especially those who were also drug-addicts On the contrary there was grudging admiration for their ability, and a peculiar snobbishness about the fact that social distinctions vanished in the common pursuit of drugs

They were completely self-centred and selfish, and showed little emotion except over their own problems While assured of what they regarded as an adequate supply of drugs—which they considered they had a right to demand—their behaviour and capacity for an average day's work often appeared more or less normal, but if this supply was not forthcoming they were overwhelmed by the need to obtain it immediately and at any cost, resorting to forging prescriptions or other crimes

The actual drugs taken are important in determining the patients' behaviour The few who were satisfied to take morphine or omnopon without cocaine were able to lead comparatively useful lives unless they became involved in selling drugs to pedlars or other addicts Most took both heroin and cocaine, and although cutting down the amount of cocaine produced no withdrawal symptoms any suggestion of reducing the dose was met by resistance and even violent reactions Fantastic stories were offered in efforts to obtain extra cocaine, but the most common pretexts were " accidents " which happened while they were preparing the cocaine for injection They also pleaded that if only the cocaine could be increased, then they would find it easier to cut down on the heroin

In six of this group of thirty-six addicts detailed histories and psychiatric treatment revealed significant differences Each had a good cultural, social, and economic background, and only one had a history of a broken home and lack of normal parental discipline and security Two were musicians, one a writer, the fourth had many friends who were musicians, and the other two were Americans who had become drug addicts here and in Paris, and who were anxious to return to America

Treatment

In the early stages of treatment, before withdrawal was started, the patients were seen in I M F 's consulting-room For the actual withdrawal they went into private nursing-homes The treatment was divided into two phases

Phase I

While the patient was being stabilised on his drugs, freed from dependence on pedlars, and helped to acquire self-respect and self-confidence, treatment was mainly psychotherapeutic

A major difficulty in the early stages of treatment was the inability of any patient to be absolutely truthful It was obvious that all of them were supplementing their legitimate supplies from the black market, and at first it was difficult for them to realise that adequate supplies could be obtained legitimately We made it clear to them that, while the ultimate aim was to free them from need for the drug, we were not prepared to go on writing prescriptions for drugs indefinitely, but they would be given a supply of drugs while they were being stabilised and freed from black-market activities, both financially and morally

A minor difficulty during this period was their inability to say simply that they had overstepped the usual amount Instead they either augmented their supplies from the black market, or produced plausible stories of accidents or losses Eventually they realised that it was better to state bluntly that too much had been used Extra supplies were prescribed to prevent them returning to the black market, which would involve them in financial difficulties, and (which is even more important) would mean a return to the degradation and humiliation of contacting the pedlars It was also made very clear that borrowing and lending would not meet with approval, but selling of drugs would be disastrous

Many of these patients were malnourished, especially those in the third group In addition they were abnormally dependent on barbiturates, especially pentobarbitone (' Nembutal ') Vitamin therapy was useful in treating the malnutrition, and the problem of the barbiturates was dealt with by substituting ' Mylomide ' (a combination of amylobarbitone and bemegride) and reducing the amount before the withdrawal treatment

The formation of abscesses after careless injection was an ever-present trouble, and frequently necessitated surgical intervention

During this phase of treatment the patients acquired enough insight into their condition to be able to cooperate, and they also acquired confidence

Phase II

During the period immediately before withdrawal treatment, chlorpromazine (' Largactil ') or perphenazine (' Fentazin ') was given to control anxiety and tension, and promethazine (' Phenergan ') to potentiate the sedatives which were necessary to promote restful sleep When the patient was in reasonably good physical condition, and for 10 days before withdrawal, concentrated vitamin (' Parentrovite ') and amiphenazole (' Daptazole ') injections were given at regular intervals

The drug was withdrawn as rapidly as possible, depending on the severity of the withdrawal symptoms The patients were assured that they would not be allowed to suffer severe symptoms, and this promise was strictly kept This was important, because if they relapsed they would not be afraid to return for further treatment No two patients reacted in exactly the same way, but all were restless, had some pain in the legs and back, and complained of weakness

As the dosage of each drug, including the barbiturates, was cut down, an effort was made not only to decrease the amount of heroin, morphine, or cocaine, but also to reduce the frequency of injections and to substitute intramuscular for intravenous injections These efforts met with varying degrees of success, especially when the ritual of the intravenous injection was threatened

By frequently substituting one pill of heroin gr $^1/_{12}$ for one of heroin gr $^1/_6$, and by very gradual reduction of the amount of cocaine, it was possible to decrease the dose considerably without the patient's knowledge and without any psychological protest It was essential meanwhile to see the patient daily, and to guard against any symptoms of withdrawal, however slight Amiphenazole given during this period was undoubtedly helpful Most addicts objected to adding the amiphenazole to their injection of drugs because it interfered with the subjective effects, but they all appeared perfectly willing to take it as tablets or separately as an injection

Generally it proved expedient to cut the dose of heroin and morphine rapidly, and to give 4-hourly amiphenazole injections during the day Cocaine was cut more slowly Perphenazine injections were given to control the anxiety and restlessness which were especially troublesome in the evening Vitamin therapy was further increased during the actual withdrawal period and parentrovite was given twice daily Fruit juice, carbohydrate drinks, and milk were given throughout

Results

With one or two exceptions all these drug-addicts are still under observation Each patient differed in response to the withdrawal of heroin, morphine, and cocaine Many were more resistant to the reduction of cocaine than to reduction of heroin or morphine The results in each group are

Group 1

All nine patients are now independent of drugs

Group 2

Three patients are completely free from dependence on drugs, two are taking small doses of morphine and are under control, and the sixth is moderately controlled but still takes morphine and cocaine and continues to deteriorate slowly

Group 3

Among this group were six addicts who proved resistant to treatment Four were psychotic, one was of very low intelligence and incapable of acquiring any insight into her condition, and the sixth was preoccupied with keeping in close touch with other addicts and supplying them, when need arose, with small amounts of heroin or cocaine at vast cost

Three other patients are not under satisfactory control, one borrows and lends drugs at intervals, and the other two almost certainly sell and then report that they have had an "accident"

Seven patients' drugs are slowly being cut down, and they intend to stop them entirely

Twenty patients have been freed from dependence on drugs Four of them who relapsed when faced with major difficulties or disaster reported back almost immediately and asked to be cleared again

In a few of the earlier cases mild convulsions and spasm of the neck and jaw muscles proved troublesome during the withdrawal phase, but preliminary reduction of the barbiturates and the other premedication almost completely eliminated this complication Visual hallucinations also were less frequent after premedication

Two or three patients experienced a short panic reaction when they realised that the heroin or morphine had been completely stopped Later they were willing to discuss plans for the future, and to accept that they must cooperate in protecting themselves from the activities of the pedlars, their associates, and also their own friends

They realised that they must either avoid conditions of stress and danger or, if this were impossible, exercise conscious discretion and aim ultimately at making a fresh start in a new environment

Convalescence was sometimes difficult to arrange except for private patients, because we were unable to find any convalescent home which would accept drug-addicts Those who were able and willing to get away from their old associates and surroundings found it easier to adjust to life, and to remain without drugs They developed a sense of wellbeing, put on weight, and were able either to undertake light work or, in most cases, to return to normal employment within a comparatively short time

Discussion

Any psychiatric therapy which offers constructive help to the addict must be based on understanding of the whole individual personality, and adjusted to individual needs It is therefore important to study the development of the personality, the hereditary and constitutional factors, and the reaction to the environment Such success as we have achieved is largely due to treating each patient as an individual, and not as one of a group Analysis of the patients' reactions and the dynamic factors involved helped them to understand themselves, their difficulties, and their pattern of behaviour in life situations The aim of treatment was to enable them to achieve the ability to deal with anxieties, to understand and accept their limitations, and to tolerate emotions which rise from frustration Insight is not enough They must try to control and strengthen personality weaknesses, for security must be based on self-reliance combined with the ability to become an integrated member of society

All the patients who have been cleared of dependence on drugs, or who are under treatment, realised that drug addiction had become the only important thing in life, and that the original reason for taking heroin and cocaine had become less important than the ritual of each intravenous injection Not one of them was a normal well-balanced personality, all had had symptoms of anxiety and lacked self-confidence, but on the surface they appeared to be leading reasonably normal lives Those who had to obtain or supplement their supplies from the regular pedlars bitterly resented the degradation of being dependent on them, and also begrudged their excessive charges for a few pills or a few grains of powder

The incentive to be free from drug addiction was strong and the patients cooperated well, especially after it had become clear that they could be freed from the pedlars and other black-market activities They later came to appreciate the factors which had been responsible for their condition, and how rapidly they were approaching the point of no return All realised that it was impossible to contemplate controlled addiction, and even the musicians accepted the possibility of living and working without the help of drugs

As a result of our interference with the activities of the black market we are now able to treat our patients with more hope of success, especially since one and then another of the best-known figures in the black market have become our patients because the market has died away

Summary

Fifty-one drug-addicts, treated between August, 1958, and March, 1960, fell into 3 groups

1 Nine patients who were originally given morphine, heroin, or pethidine for adequate medical reasons had continued to obtain supplies of the drug All are now clear of dependence on drugs

2 The oldest group of six patients came from a higher social and cultural level Three are now clear of dependence on drugs, two are still taking small doses, but they are under control and intend ultimately to stop, and the sixth is under moderate control but seems likely to deteriorate slowly

3 Of the largest group of thirty-six patients, aged 18–32 years, twenty have been cleared of dependence on drugs, ten are still under treatment, and six have proved resistant to treatment

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" The ability to provide the kind of setting in which those who are mentally ill or emotionally disturbed can still function to the best of their abilities, without the stigma that traditionally attaches to the word 'mad' is an important challenge to the contemporary industrial society of the Soviet or American type The main contribution the Soviets have made, lies, probably, in their concepts of not condemning psychotic patients to the idle, demoralizing, de-socializing, untherapeutic and wasteful life of the chronic patient in the large mental hospital Concomitant with this approach is the bringing of psychiatric care into the community, even into the patient's home if necessary, and the linking of this treatment with the general network of medical facilities maintained under a system of socialized medicine By contrast, it may be that their contribution to the treatment of the neuroses is hampered both by the collectivistic nature of their social order and philosophy, and the dogmatic intolerance of schools that do not fit their theoretical and ideological commitments"—MARK G FIELD, PH D , *Social Problems*, 1960, 7, 277

Medical Societies

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE

AT a meeting in London on Dec. 8, Sir William MacArthur, the president, on behalf of the American Society of Tropical Medicine and Hygiene presented the Walter Reed medal to Sir Gordon Covell.

Hookworm Disease and Anæmia

Dr E. VAN OYE (Belgium), in a paper read in his absence by Dr L. G. GOODWIN, drew attention to the high incidence of hookworm infection among inhabitants of the Belgian Congo and Ruanda-Urundi and the high degree of morbidity ascribed to the infection. Bephenium ('Alcopar', Burroughs Wellcome) had been found to be effective, non-toxic, and easy to administer without previous preparation. The drug was, therefore, very suitable for mass treatment.

Dr G. J. STOTT had carried out an investigation in Mauritius, on behalf of the World Health Organisation, following a preliminary survey there by Prof. A. W. Woodruff. Dr Stott had found that hookworm infection with hypochromic microcytic anæmia was very common. Such infection had been present in 88% of 284 anæmic patients, and the anæmia responded well to iron therapy, significant improvement being obtained with as little as 6 mg. of iron per day even without prior anthelminthic treatment. The national diet provided only 10.2 mg. of iron per head per day, and among certain groups the amount was as low as 6 mg. The diet was in fact so low in iron that even moderate hookworm loads could cause sufficient blood-loss to precipitate anæmia. Enrichment of the national diet with iron was likely to prove the most effective single public-health measure against anæmia in Mauritius.

Dr HENRY FOY and Dr ATHENA KONDI reported that the use of radioactive iron and chromium had established that intestinal blood-loss from infections with 1000–3000 hookworms ranged from 50 to 200 ml. per day. Lack of correlation between the worm load and the presence of anæmia could usually be explained by recent administration either of iron or of vermifuges. Intestinal blood-loss could be reduced to nil by removing the worms, but unless iron therapy was also given no improvement in the hæmatological picture would result because worming did not replace depleted iron stores. Parenterally administered iron had never been required in their series, and gastrointestinal upsets from oral iron had been rare. Blood-transfusion had seldom been required. In some the hæmoglobin could not be raised above 12 g. per 100 ml., and in such cases some other intercurrent infection was usually present. Dr Foy emphasised the value of periodic vermifuges, in addition to iron treatment.

Prof. A. W. WOODRUFF, opening the discussion, made three points. The first concerned the importance of work on anæmias in the tropics. This importance derived from their extraordinary prevalence, from the clearer idea of their causation on a public-health scale now that malaria was eradicated from so many regions, and from the coming of the World Health Organisation which had provided a stimulus to acquire knowledge on which could be based schemes for elimination of anæmia. His second point concerned the necessity to take into account the time which might be required for hookworm infection to deplete body stores of iron. Until these were depleted, patients might have heavy hookworm infections without anæmia. This had to be noted when considering correlations between hookworm infection and anæmia. Thirdly, it was important to remember that in the tropics anæmias often had a complex ætiology. Patients were commonly infected with several parasites and might also suffer from liver damage and malnutrition.

Dr O. D. STANDEN drew attention to the resurgence of interest in hookworm infections, partly owing to the introduction of bephenium as a vermifuge.

Sir SELWYN SELWYN-CLARKE doubted the value of dietary fortification with iron so long as patients were being reinfected with hookworms. He emphasised the importance of raising the general standard of hygiene.

Sir GEORGE MCROBERT, however, argued that, though latrines could be provided, it was in many places a time-consuming task to educate the population to use them, and, so far as anæmia was concerned, more good could be brought about by administration of iron costing a few pence than by costly sanitary schemes.

Prof. GEORGE MACDONALD supported the view that supplementation of the dietary iron was an essential means of eradicating iron-deficiency anæmia, and he emphasised that critical analysis still left doubts concerning the causal relationship between hookworm infection and anæmia. The connection might well be there, but it had not yet been proved, and other causes of iron deficiency and of anæmia had to be carefully considered.

HEBERDEN SOCIETY

THE society met in London on Dec. 2 and 3.

In a Heberden oration Dr JOSEPH J. BUNIM (Bethesda) described 40 cases of Sjogren's syndrome. All but 1 were in women, with a mean age of 50 years. The diagnosis was based on dryness of the eyes, nose, mouth, or throat and on keratoconjunctivitis sicca, xerostomia, and rheumatoid arthritis, at least two of these three conditions being present in all cases. 21 of the 40 patients gave a history of previous drug sensitivity. The serum-albumin was reduced, and the serum-globulin was raised above 3.5 mg. per 100 ml., this increase was particularly of the $_2$ fraction, which on analytical ultracentrifugation proved to be the 7S type, and the amount of this fraction was raised in most patients with the keratoconjunctivitis sicca complex alone. The test for the rheumatoid factor using bentamite flocculation on whole serum was positive in all cases, and using the sensitised-sheep-cell agglutination test on the euglobulin fraction it was positive in 83% of cases. Anti-nuclear factor was found in 77% of sera, it was present in all cases with myopathy, all cases with keratoconjunctivitis sicca and xerostomia alone, and 60% of cases of rheumatoid arthritis and keratoconjunctivitis sicca, but in only 13% of a control group of rheumatoid arthritis without keratoconjunctivitis sicca. L.E. cells were found in only 3, and these were all cases of rheumatoid arthritis. A high prevalence of complement-fixing antibodies with liver homogenate was found, particularly in the cases of pure keratoconjunctivitis sicca. As the histological changes in Hashimoto's disease closely resemble those in Sjogren's syndrome, examination for thyroid disease was carried out. By the tanned-red-cell technique, thyroglobulin antibodies were detected in 11 of the cases. In only 5 was there evidence of thyroid disease, and in 2 of these section of the gland showed changes consistent with Hashimoto's thyroiditis. Of eleven patients' families studied, eight had 2 or more members with thyroglobulin antibodies, whereas of six control families only one exhibited this feature.

Dr Bunim concluded that, like systemic lupus erythematosus and rheumatoid arthritis, Sjogren's syndrome was a multi-system disease, and the high prevalence of circulating antibodies to various tissue components in Sjogren's without rheumatoid arthritis was reminiscent of systemic lupus erythematosus. The pathogenic implications of these antibodies was obscure.

Sacroiliac Joints in Juveniles

Dr MARY CARTER (Canadian Red Cross Memorial Hospital, Taplow) said that dissection of four normal sacroiliac joints from children had shown broad, smooth, sacral cartilage and thinner, irregular iliac cartilage with radial "splits" bounding a narrow joint space which was deeper in the anterior part of the joint, the most posterior part being largely filled with fibrous tissue. In the case of a child with rheumatoid arthritis who had died at the age of 9 years and in whom X-ray examination had shown a doubtfully abnormal sacroiliac joint cartilaginous fusion of this right joint was found without any sign of inflammatory tissue. This might have resulted from the mechanical factor of severe hip disease or previous prolonged immobilisation. In the case of a 20-year-old patient with rheumatoid arthritis, whose pelvic X-ray was normal, post-mortem examination showed changes in both sacroiliac joints with destruction of iliac cartilage and invasion of bony spaces with granulation tissue containing plasma cells and lymphocytes.

Still's Disease

Dr BARBARA ANSELL and Prof E G L BYWATERS (Taplow) had in January, 1959, begun to review 264 cases which had been referred as Still's disease. Hitherto 43 had been classed as probable Still's disease. In the follow-up period a definite diagnosis has been made in 20: psoriasis (2), ulcerative colitis (2), further features of classical Still's disease (5), ankylosing spondylitis (2), rheumatic fever (2), osteochondritis (2), systemic lupus erythematosus (1), dermatomyositis (1), Raynaud's syndrome (1), infectious arthritis (1), scleroderma (1). The remaining 23 cases fell into three main groups: (*a*) those with systemic manifestations resembling Still's disease in which rheumatoid arthritis was slight and joint residua were absent; (*b*) those with transient polyarthritis with slight residua; and (*c*) those with less than four joints involved in which residua were common and which might represent a mild form of the disease.

Intervertebral-disc Degeneration

Dr J S LAWRENCE (Manchester) and Dr JOAN BREMNER (Leeds) had found in population samples in Leigh and Wensleydale that cervical-disc degeneration was uncommon below the age of 25, but the prevalence rose steadily with age, and such degeneration was more common and severe in males of all age-groups. The maximum frequency was at C5. The dorsal region was the most usual site of degeneration, and here it tended to occur earlier and more severely in females than in males, with D7 most commonly involved in females and D8 in males. The lumbar spine was not X-rayed below the age of 35, and by then disc degeneration was found in 35% of males, with L3 most commonly involved; as in the cervical region, involvement was more common and more severe in males. There was a significant relationship between cervical-disc degeneration and neck, shoulder, and brachial pain, the association being greater in females and under the age of 45. In males lumbar-disc degeneration correlated well with incapacity and with back, hip, and sciatic pain. Differences were noticed between urban and rural populations in that the disease was more evenly distributed between the sexes in the rural area and in this area the changes in the lumbar region were earlier in onset.

Ten-year Follow-up of Rheumatoid Arthritis

Professor BYWATERS, Dr M CURWEN, Dr E DRESNER, and Dr A ST J DIXON (Hammersmith Hospital) had followed up 250 cases of rheumatoid arthritis first seen between 1939 and 1948, 125 of them within one year after the onset. As in other series females predominated, and the mean age of onset was about 45. At the ten-year follow-up, 78 of the 250 patients were dead, 76 were in the top two functional grades, and 96 were in the lower three functional grades. Further follow-up information revealed that 131 were now dead. It appeared that in patients who were going to die death was preceded by reduction of functional capacity which was not necessarily from a cause associated with the rheumatoid arthritis—e.g., it might arise from coronary thrombosis. The overall mortality was greater than the expected. Younger patients did better than older, as did males and also those with asymmetrical involvement and fewer joints involved. A negative differential agglutination test (D.A.T.) at follow-up was a good prognostic feature, and females with a negative D.A.T. did better than females with a positive D.A.T. The diagnosis of psoriasis also seemed to be associated with a better prognosis. Death when it occurred was very rarely due to specific complications of the disease but tended to occur from usual causes before the expected age.

Reviews of Books

Clinical Gastroenterology

F AVERY JONES, M.D., F.R.C.P., physician; J W P GUMMER, M.S., F.R.C.S., surgeon, Central Middlesex Hospital. Oxford: Blackwell Scientific Publications. 1960. Pp. 652. 70s.

THE appearance of a new book by authors distinguished in their subject is always important and exciting. Will they present their experience in a way intended to provoke argument, controversy, and thought, or more factually? Those who expect here a treatise in the first category have mistaken the implication of the title—the emphasis is "clinical"—for this is a work written within the tradition of the British textbook. Each subject is introduced with a list of possibilities either in the pathological or diagnostic sense and followed by amplification in the matter of symptoms, signs, and management in sections devoted to the alternatives. There are exceptions to this general plan; it is inapplicable to the chapters on motility and on torsion and volvulus; it is avoided when trauma is considered. Half the space of the first dozen pages is absorbed by lists. Those who complain that this is tiresome reading should reflect that it is hard to make works of reference readable—and this is a work of reference despite its deceptive size, in which there is frequent allusion to a highly selected bibliography. Furthermore, it is not in any other way hard to digest, for the text is written with admirable clarity, though the type does seem a bit small.

What is lost in personality is gained in orthodoxy; the reader knows that he is treading the right path, that armed with this knowledge he will not go far wrong. The book is therefore appropriate for the postgraduate student rather than the expert. A work, avowedly, of instruction rather than inspiration, it is welcome because it fills an important gap, and valuable because of the industry of its authors in covering the whole of gastroenterology (with the exception of proctology) as seen in the average clinic.

The Femoral Neck: Function, Fracture Mechanism, and Internal Fixation

VICTOR H FRANKEL, M.D., associate professor of orthopædic surgery, University of Uppsala. Stockholm: Almqvist & Wiksell. 1960. Pp. 120. Sw. kr. 32.

WHEN Smith-Petersen, in 1931, described the treatment of hip fractures by the insertion of a three-flanged nail, it seemed that a solution had been found for what had often been called 'the unsolved fracture'. Unfortunately recent figures show that, even in the best hands, some 20% of femoral-neck fractures so treated do not unite, and that aseptic necrosis supervenes in about the same proportion of those which do.

This monograph cites some of these figures and recounts briefly the history of the nailing operation before Smith-Petersen (von Langenbeck first nailed a hip in 1878 and Lister did so soon after). Then follows a list of some fifty devices produced during the past thirty years, each of which has been claimed as an improvement on the appliance used by the Boston team. The author's own work has involved a study of the mechanisms of femoral-neck fractures, and of the circumstances under which devices for internal fixation fail, by the use of 'Stresscoat' and strain-gauge techniques. None of the appliances examined were found ideal in form or substance, and, as the author points out, even if one were contrived it could not be placed in the best line for securing the fracture, since this line changes with movements and muscle contractions.

Much of this attractively produced book presupposes a considerable knowledge of mechanics, but it indicates, even to the least mechanically minded, some of the problems which still beset the management of these injuries

A Synopsis of Public Health and Social Medicine

A J Essex-Cater, MRCS, DCH, DPH, DIH, FRAI, administrative medical officer of health, City of Birmingham Bristol John Wright 1960 Pp 576 55s

In a foreword to this volume in the well-known series of synopses, designed to meet the requirements of undergraduate and postgraduate medical students, nurses and others, Prof J M Mackintosh recalls that in the past twenty years developments in social medicine, health education of the public, and mental health have broadened the scope of preventive medicine to an unprecedented degree Much of the text is devoted to a description of the epidemiology of infectious and non-infectious diseases Other sections deal with the history of public health the organisation of the National Health Service medical statistics, occupational health, environmental hygiene, the care of mothers and young children, the school health service and mental health The book ends with a chapter including notes on heredity, the atomic age, and the disposal of the dead There are some minor errors, and it has not been possible to include some of the most recent legislation, reports, and statistics, but with these reservations the volume can be recommended as a useful summary of public health and social medicine

The Exercise Book of Dr Christobel Mendez

Translated by Francisco Guerra Editor Frederick G Kilgour Baltimore Waverly Press 1960 Pp 122 $10

"Galen says that medicine is the science of the healthy the sick, and the chronic who are neither" So begins the first printed book on the merits of exercise ever written by a physician, and we may judge from the remainder of the work that its author, like many of his later counterparts, found that it was the last-named amongst his patients who taxed him most

Published in 1553, the book belongs to the great era of scientific writing which had been heralded by the appearance of Vesalius's *De Fabrica* ten years before, and coincided with the description of the pulmonary transit by Servetus in *Christianismi Restitutio* It is not, of course, to be compared with either of these volumes Mendez has no original discoveries to announce He subscribes unreservedly to the old Galenic doctrines and provides further evidence of his credulity by recounting several highly improbable anecdotes With all his faults, though, he still makes engaging reading In part because of his sensible and lucid advice upon a hygienic way of life in part because of his apposite observations upon several matters quite unconnected with medicine ("Brother," he says, with reference to duelling, "have good temper, and always look at the tip of the sword of your enemy, and you do not need anything else")

In its present form the treatise has been translated, with a complete reduction facsimile of the old Spanish text appended We hope its appearance will be the means of acquainting a wider audience with a book of which, in the original, there are only three known copies

Diagnosis and Treatment of Tumours of the Chest

Editor David M Spain New York and London Grune & Stratton 1960 Pp 371 104s

If this were the only book on the subject it would be easy to review it wholly favourably, for it covers a large area adequately and provides an easily readable account which is undoubtedly useful to clinicians studying chest tumours Unfortunately, as with most composite works, it is of uneven merit, with excellent chapters next to ones less good The variation extends beyond mere style and exhaustiveness The manner in which the references are dealt with varies from chapter to chapter Some authors have used the numerical system, making reference to source material easy, others have given the author's name and date in the text, or the name only In some chapters the references are arranged alphabetically, in others numerically, and in some there are names mentioned in the text but not in the references This variation is a drawback in a book of this kind, for many chapters are of little value as sources of reference to the more knowledgeable readers, and others may seem too well documented and exhaustive for the postgraduate student There seems to be a lack of clearly defined purpose in the book's construction, which is a pity, for it contains much of value and much good medical writing

Manual of Hand Injuries (2nd ed Chicago Year Book Publishers London Interscience 1960 Pp 400 83s) — The writings of Kanavel and Bunnell gave America a lead in the literature of hand surgery which only a few British authors have yet challenged This book of Dr H Minor Nichols is not the least of the volumes which are maintaining this advantage It is short, compact, exceedingly comprehensive, and intensely practical Indeed its scope is so wide, and its instructions so detailed that the introductory caution—that the surgeon dealing with a hand injury must not be tempted into essaying orthopædic or plastic feats for which he has not been specially trained—seems very necessary Fractures and dislocations often relegated to a brief final or penultimate chapter, are discussed at length It is evident that the finger-traction devices of earlier days are now being discarded in favour of intramedullary Kirschner wires, and more rapidly in the United States than in this country In general, methods advocated throughout are those in favour here, and great emphasis is placed on conservative manœuvres to be adopted in the face of apparently irreparable damage (The author admits the limitations of vein grafts in an ischæmic arm, and urges deliberate bone shortening to permit end-to-side arteriorrhaphy) It seems strange, though, that whenever local anæsthesia is mentioned, the agent suggested is procaine, which most British surgeons abandoned for lignocaine several years ago This book can be commended in the highest terms as an excellent resumé of the advances which have been made by the opposite side in a subject where there is strong and very friendly rivalry

Obstetrics (12th ed Philadelphia and London W B Saunders 1960 Pp 1098 £5 19s) —In revising this well-known book, based on the original text of Joseph B De Lee, Dr J P Greenhill has had much help from 23 contributors Several new sections and chapters have been added Increased attention is paid to obstetric factors which may result in fœtal deformity or cerebral palsy, and two of the new chapters are devoted to these important subjects Like its predecessors, this edition is beautifully produced, and there are many new photographs and diagrams The work gives a balanced account of modern obstetric practice, and its continued popularity is assured

Marriage and Periodic Abstinence (2nd ed London Longmans, Green 1960 Pp 86 10s 6d) —The theory of periodic abstinence is based on the assumption that ovulation takes place once during each menstrual cycle and that if this time can be identified by temperature readings, and intercourse avoided, then pregnancy will not ensue For many people this is the only permissible means of avoiding a succession of pregnancies and it is important that the knowledge should be widely available The intelligent lay person should be able to follow Dr J G H Holt's explanation and instructions, here adapted by Dr John Marshall, but these could, with advantage, be presented more simply and clearly Readers with no religious bias and with complete freedom of choice are likely to disagree with the contention that periodic abstinence is the most satisfactory and effective means of birth control available today

Textbook of Surgical Pathology (8th ed London J & A Churchill 1960 Pp 704 75s) —A virtue of this popular work by Prof C F W Illingworth and Mr B M Dick lay in its brevity, for it enabled the student to encompass the subject within reasonable time This it still does, but in this eighth edition the bibliography, which is surely important in any concise work of this kind, has been discarded

THE LANCET

LONDON 24 DECEMBER 1960

More on Leukæmia and Radiation

EVER since the reports of increasing incidence of leukæmia in Japan after the atom-bomb explosions, much attention has been paid to the possible connection between exposure to radiation and the later development of leukæmia In this country research was stimulated by the suggestion of ALICE STEWART and her co-workers [1] that acute leukæmia in childhood was more likely if the mother had been subjected to much X-ray exposure, say for pelvimentry, during pregnancy and by the demonstration by COURT-BROWN and ABBATT [2] that the incidence of leukæmia was definitely increased among patients treated with deep X-rays for ankylosing spondylitis Accumulating evidence has, on the whole, failed to substantiate the danger of maternal X-radiation to the fœtus, at least in so far as the incidence of leukæmia is concerned The latest of these investigations, carried out by COURT-BROWN, DOLL, and BRADFORD HILL,[3] was extensive Information was gathered about 39,166 mothers who were known to have had abdominal or pelvic diagnostic X-rays in eight hospitals in London and Edinburgh between 1945 and 1956 In 9 of the children of these mothers leukæmia had developed by the end of 1958, whereas the estimated expected number was 10 5 It has been suggested that exposure during the first half of pregnancy may be more dangerous than in the second half 750 women studied by COURT-BROWN had been irradiated during the first three months of pregnancy but in none of their children had leukæmia developed during an average follow-up of six years COURT-BROWN et al review the published data from five other surveys and point out that the evidence is conflicting, in three of these surveys the proportion of mothers who had been irradiated during pregnancy was greater among the mothers of leukæmic children than among mothers of control children, in one there was no difference, and in the fifth the mothers of leukæmic children had been less often irradiated than the controls COURT-BROWN and his colleagues conclude from their own data that " there is no evidence of any disproportionate occurrence of leukæmia among the children who had been most heavily irradiated nor among the children who had been irradiated early in intrauterine life " Taking their data together with the published results they do not believe that an increase in leukæmia among children of mothers who have had abdominal irradiation during the pregnancy has been established A very similar conclusion has been reached by LEWIS [4] who utilised the records of Queen Charlotte's Hospital in London

Another possible way in which radiation may induce leukæmia is by exposure to radioactive isotopes for the treatment of disease Radioactive gold and yttrium have been used in the treatment of tumours, but the two diseases in which large numbers of patients have been treated are thyrotoxicosis treated with radioiodine (^{131}I) and polycythæmia vera treated with radiophosphorus (^{32}P) POCHIN [5] has reviewed the 18 known cases of leukæmia that has developed in patients previously treated with radioiodine for thyrotoxicosis, the type of leukæmia was known in 17 cases, and was acute in 13 10 of these cases occurred in the U S A , 4 in Canada, 3 in this country, and 1 in Austria. POCHIN estimates that about 60,000 patients have been so treated in these four countries In such a population an estimate based on the reported incidence of leukæmia suggests that about 21 (14–28) cases would occur whether or not radioiodine was given There are, of course, considerable uncertainties in such estimates, patients relieved of their symptoms may cease to attend the clinic, and if leukæmia develops later they may be missed A routine blood-count before starting treatment may reveal early cases of leukæmia that would otherwise appear as cases developing after treatment, POCHIN notes that in his experience 3 cases were detected in this way But, making allowances for such uncertainties, POCHIN justifiably suggests that there is no evidence from present records that radioiodine treatment is inducing leukæmia. The effect of radiophosphorus treatment on the incidence of a leukæmic transformation in polycythæmia vera is less easily assessed because the disease can naturally terminate in leukæmia, but in many cases the terminal stage is really a leukæmoid reaction, and SCHWARTZ and EHRLICH [6] found only 1 acceptable case of leukæmia in a critical study of 83 cases WASSERMAN [7] in 1954 reported 7 cases of leukæmia among 64 cases of polycythæmia, and LAWRENCE [8] in 1955 reported 16 among 231 SZUR et al [9] have described 2 such cases among a group of 90 treated with radiophosphorus, but both patients had received X-ray therapy earlier in their illness Other methods—chemotherapy and venesection—are also used for the treatment of polycythæmia WALD et al [10], for example, report good results with 'Myleran' (busulphan), and in time we should have a series of patients who have not received radiation treatment and can therefore be used as controls At present no firm conclusion can be reached about the relative incidence of leukæmia in polycythæmic patients who have or have not been irradiated

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[1] Stewart A Webb, J , Giles D , Hewitt D *Lancet*, 1956 ii 447 See *ibid* 1955 ii 990

[2] Court Brown W M , Abbatt J D *ibid* 1955 i, 1283

[3] Court Brown W M Doll R Hill A B *Brit med J* No 30 1960 p 1539

[4] Lewis T L T *ibid* p 1551

[5] Pochin E E *ibid* p 1545

[6] Schwartz S O Ehrlich L *Acta hæmat Basel* 1950 4 129

[7] Wasserman L R *Bull N Y Acad Med* 1954 30 343

[8] Lawrence J H Polycythemia Modern Medical Monographs New York, 1955

[9] Szur L, Lewis S M Goolden A W G *Quart J Med* 1959 28 397

[10] Wald N Hoshino T , Sears M E *Blood* 1958 13 757

A third source of exposure to irradiation is radioactive tracers, which are being used increasingly in research and diagnosis[11] In hæmatology radioactive chromium (^{51}Cr, half-life 27 days) is used for determinations of blood-volume, red-cell survival, and blood-loss in the gastrointestinal tract Diisopropylfluorophosphonate labelled with ^{32}P has been used for estimating the survival-time of platelets For studies of iron metabolism radioactive iron is extensively used—usually the isotope ^{59}Fe with a half-life of 46 days Studies of the absorption of vitamin B_{12} have been greatly aided by the use of a vitamin labelled with radiocobalt, at first the isotope ^{60}Co (half-life 5 3 years) was used, today the isotope ^{58}Co (half-life 71 days) is preferred ANDERSON et al[12] have lately studied folic-acid excretion by using folic acid labelled with tritium (^{3}H, half-life 12 3 years) The doses of radioactivity applied for any one estimation are carefully adjusted to be well within safety limits But over a period of time a patient may receive a sizeable dose, perhaps for investigation of disorders in more than one system, and the life of some of the isotopic tracers is far from short For these reasons it is essential, as HAYTER[11] emphasises, that proper records should be kept now, so that undue exposure can be avoided The second report of the Adrian committee, which appeared[13] recently, was concerned only with genetic doses, and the estimated annual genetic dose per person from all present uses of radioisotopes in medicine was only 0 18 mr The committee will doubtless have something to say later about the somatic effect of isotopes

Perhaps we are over-sensitive about the dangers of radioactive materials The answer to questions about the use of radiation techniques and treatment is surely, as the Adrian committee emphasises, that they should be used reasonably when clear benefit can be expected, and that they should not be used for routine investigation or treatment when alternatives not involving irradiation are to hand It would certainly be foolish to abandon radiology in pregnancy, because this may not infrequently be the only means of ensuring safety for mother and child In some cases of thyrotoxicosis treatment with radioactive iodine may be more suitable than surgery or administration of anti-thyroid drugs, and it apparently carries no greater risk For polycythæmia chemotherapy can be tried before embarking on treatment with ^{32}P With regard to radioactive tracers, HAYTER proposes that they should not be used unless there is a clear case for them, and for ordinary diagnostic work

> " it is quite often reasonable to dispense with an isotope ' test ' when an equally informative conventional test is available For instance, when documentary evidence is needed ' for the record ' in a clear case of thyrotoxicosis, it seems proper to estimate the B M R rather than ^{131}I uptake, since the more sensitive differentiation possible with the latter is not needed "

This good advice reminds us that methods involving radioactive materials for investigation or treatment should not be used only because they are easier than conventional methods

Hartnup Disease

IN 1956 DENT and his colleagues,[1] in a paper entitled " Hereditary pellagra-like skin rash with temporary cerebellar ataxia, constant renal aminoaciduria, and other bizarre biochemical features ", defined a new syndrome which has since become known as Hartnup disease, after the affected family The full clinical picture appeared in two of four affected siblings who were subject periodically to a photosensitive rash, apparently identical with that of true pellagra, on exposed areas of the body, its appearance was sometimes associated with severe but fully reversible cerebellar ataxia All four patients had a pronounced aminoaciduria of characteristic and unique paper-chromatographic pattern, and an abnormally large output of certain indolic compounds Since the disease was first described, nine further cases have been recognised,[2–7] so that the natural history is now better known This recessive hereditary metabolic disorder manifests itself in childhood, and, unlike most other hereditary metabolic conditions, tends to improve with increasing age all four affected members of the original family have been completely asymptomatic since 1956[8] The disorder is probably less rare than might be expected from the smallness of the number of cases so far described, for some of those affected may be symptom-free, and their biochemical abnormality would be unlikely to be uncovered unless they had more severely affected siblings Although the rash may respond to nicotinamide therapy, dietary sources of this vitamin are apparently adequate DENT and his colleagues[1] thought it much more likely that an endogenous block in the conversion of tryptophan to nicotinic acid was present They had difficulty, however, in finding a unifying hypothesis by which to correlate all the clinical and biochemical features

MILNE et al ,[8 9] having made some careful observations on two affected members of the original family, have provided an elegant and convincing hypothesis which goes far towards explaining the abnormalities in metabolism of indolic and possibly of other aminoacids too The generalised aminoaciduria of renal tubular origin, without evidence of other defects of renal tubular function, suggested to them a specific defect in the transfer of aminoacids from the glomerular filtrate across the proximal renal tubular cells into the tubular capillary blood Such a transport defect might not be confined to the renal tubular cells They therefore designed an investigation to explore the possibility of a similar defect, of tryptophan transport in particular, in the gut, and they demonstrated delayed and incomplete jejunal absorption of L-tryptophan The high output of indole metabolites for many hours after tryptophan ingestion could thus be explained by the action of intestinal bacteria on an abnormally large fraction of tryptophan reaching the colon. In the patients with Hartnup disease, but not in controls, tryptophan was found in the fæces after an oral load. The findings after ingestion of DL-tryptophan (D-tryptophan was not available) suggested delayed absorption of D-tryptophan also. This is further evidence that the absorption of D-aminoacids from the gut is not an entirely passive process.[10] These observations are complemented by the important studies of SHAW et al.[11] who found that in Hartnup disease ingestion of L-tryptophan produced no increased urinary output of indole metabolites when the gut had previously been sterilised with neomycin.

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[11] Hayter, C J *J clin Path* 1960 13, 369
[12] Anderson, B , Belcher, E H , Chanarin, I , Mollin, D L *Brit J Hæmatol* 1960 6, 439
[13] See *Lancet*, Dec 10, 1960, p 1285

[1] Baron, D N , Dent, C E , Harris, H , Hart, E W , Jepson, J B *Lancet*, 1956 ii, 421
[2] Hersov, L A *J ment Sci* 1955, **101** 878
[3] Hickish G W *Arch Dis Childh* 1955, 30, 195
[4] Jonxis, J H P *Ned Tijdschr Geneesk 1957* **101**, *569*
[5] Henderson, W *Arch Dis Childh* 1958, 33, 114
[6] Weyers, H Bickel, H *Klin Wschr* 1958, 36 893
[7] Hersov, L A , Rodnight, R *J Neurol Neurosurg Psychiat* 1960, 23, *40*
[8] Milne, M D , Crawford M A , Girão, C B , Loughridge, L W *Quart J Med* 1960, 24 407
[9] *Milne, M D , Crawford, M A , Girão,* C B , Loughridge, L *Biochem* 1959, 72, 30P

If the exacerbations of cerebellar ataxia stem from intoxication by indole metabolites, gut sterilisation is a rational method of treating such attacks. MILNE et al.,[5] thinking in terms of intoxication by retained indolic acids, suggest that alkalinisation of the urine would provide an easy and innocuous method of treatment, for they have previously shown[12] that excretion of indoleacetic acid is facilitated in alkaline urine. A possibility which seems equally likely is that the neurological symptoms arise from tryptamine intoxication.[13] Large amounts of tryptophan stagnant in the gut probably give rise to increased production of this amine from the action of intestinal bacterial decarboxylases.[14] When further patients are investigated, a search for abnormal urinary amines should prove fruitful.

DENT and his colleagues[1] originally suggested that an enzyme in the tryptophan/nicotinic-acid pathway might be deficient, and other workers[15] have cast tryptophan pyrrolase in this role. This enzyme is responsible for splitting the 5-membered section of the twin-ringed indole nucleus of tryptophan—the first step in the nicotinic-acid pathway of tryptophan metabolism. Although MILNE et al.[5] sought to test this hypothesis by estimating metabolites of this pathway after oral tryptophan, the information they obtained is probably equivocal because of the jejunal transport defect which was present. An intravenous tryptophan load will probably be necessary in future work designed to elucidate this problem, although the possibility of a transport defect in other body-cells must be kept in mind in interpreting the results.

Despite one or two inconsistencies (such as the inability of MILNE et al.[5] to find evidence of impaired absorption of tyrosine, another aminoacid represented in the aminoaciduria) which probably arise from the inherent difficulties of biological experimentation, the transport-defect hypothesis seems to fit the observed evidence best and accords well with the "one gene, one enzyme" concept of modern biochemical genetics. If the aminoacids excreted in great excess in Hartnup disease all have a similar transport mechanism, then a different transport mechanism or mechanisms probably exist for the unaffected aminoacids. We venture to predict that clinical conditions analogous to Hartnup disease, involving a transport defect of some or all of the basic aminoacids, sulphur-containing aminoacids, prolines, and glycine will be found if watch is kept for them.

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[10] Jervis E. L., Smith D. H. J. Physiol. 1959, 147, [illegible]
[11] Shaw K. N. F., Redlich D., Wright S. W., Jepson J. B. Fed. Proc. 1960, 19, 10.
[12] Milne M. D., Crawford M. A., Girao C. B., Loughridge L. W. Clin. Sci. 1960, 19, 165.
[13] Sjoerdsma A., Oates J. A., Zaltzman P., Udenfriend S. J. Pharmacol. exp. Ther. 1959, 126, 217.
[14] Weissbach H., King W., Sjoerdsma A., Udenfriend S. J. biol. Chem. 1959, 234, 81.
[15] Nemeth A. M., Nachmias V. T. Science, 1958, 128, 1085.

Annotations

QUADRUPLE VACCINE

WE have already argued that the problem of preventing poliomyelitis, diphtheria, whooping-cough, and tetanus might be solved by administering a combined prophylactic early in life.[1,2] In this way the cost of administration would be reduced and the proportion of children immunised would be increased, because parents, doctors, and children dislike the large numbers of injections involved in giving each prophylactic separately. The present rate of immunisation is too low to give much confidence that the incidence of these diseases will remain as low as it now is.

One way to ensure that children are immunised is to start the series of inoculations in the first week of life, when the mother is in hospital or under medical care at home. Unfortunately, young infants respond less well to antigens than older children. Furthermore, antibodies transmitted from the mother interfere with the acquisition of active immunity after immunisation against diphtheria[3] and poliomyelitis.[4] It is important, therefore, to establish that all the components of a quadruple vaccine are effective at the age at which it is to be administered. Brown and Kendrick[5] have reported the results of administering quadruple vaccine to children aged 2–4 months. The response to the poliovaccine was poor, almost certainly owing to the presence, in most infants, of maternally transmitted antibodies. (The wise practice of immunising pregnant women with poliovaccine is increasing this problem.) It was also found that the response to the pertussis component was poor, 14 out of 43 children without antibodies failing to respond. Brown and Kendrick therefore advocate early immunisation with pertussis vaccine alone, this disease being especially severe under 1 year, and administration of a triple poliomyelitis, diphtheria, and tetanus prophylactic at about 1 year.

In an effort to overcome the poor response of young children, three main approaches have been tried: the inclusion of adjuvant, more and larger doses, and more concentrated vaccine. Quadruple vaccine with aluminium phosphate has lately been reported to be very effective in children under 6 months.[6] The prevalence of maternal antibodies was not very high in this series of children, and 83%, 80%, and 73% responded to poliovaccine of types 1, 2, and 3 respectively, but the geometric mean titres were low. In children over 6 months it was found that the response to poliovaccine in the quadruple vaccine was superior to the response to plain polio vaccine. The responses in children under 6 months were also good (over 85%) to the diphtheria, tetanus, and pertussis components. Perkins et al.,[7] who first noted the inhibiting effect of passively transferred antibodies on the response to poliovaccine,[4] have devoted much effort to overcoming this difficulty Although three doses proved superior to two doses, it was not until concentrated vaccine was used that satisfactory responses were obtained in children 1 week old The concentrated vaccine (' Purivax ', Merck Sharp & Dohme) is very much more potent than vaccine now used in this country and elsewhere Results obtained in Israel [8] with vaccine slightly more potent than the usual support the idea that children with maternally transmitted antibodies can be immunised with a potent poliovaccine These results indicate that the goal of a satisfactory quadruple vaccine for use in the first weeks of life may be attainable, but the findings of Brown and Kendrick [6] show that the pertussis component may have to be modified To give the fullest possible protection, pertussis vaccine must be given early in life, and it is known that the response, measured by agglutinin titre (not by a mouse protection test, which assays the antibodies concerned with protection [9]) is greater if an aluminium-phosphate adjuvant is used

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[1] Lancet, 1960, i, 1057.
[2] Ibid. Sept. 3, 1960, p. 531.
[3] Barr M., Glenny A. T., Randall K. J. Lancet, 1950, i, 6.
[4] Perkins F. T., Yetts R., Gaisford W. Brit. med. J. 1958, i, 68.
[5] Brown G. C., Kendrick P. L. Amer. J. publ. Hlth, 1960, 50, 1529.
[6] B[illegible] D. E., Wheeler J. W., B[illegible] P. A., P[illegible] R., S[illegible] F. P. J. Amer. med. Ass. 1960, 174, 1166.
[7] Perkins F. T. Paper read at symposium on Standardisation of Antibody Production, British Society for Immunology, Nov. 25, 1960.

Living attenuated poliovaccine has also been found to be less effective early in life, but this has been ascribed to immunological immaturity rather than to the inhibiting effect of maternal antibodies [10] This is unlikely to be overcome by a larger dose, since no antibodies appear despite multiplication of the virus in the alimentary tracts of the infants Poliomyelitis being relatively rare under 1 year, it may be said that there is no reason to try and immunise children against it early in life But such immunisation is desirable for three reasons first, it is easier to persuade the parents to have the child immunised at that stage, secondly, poliomyelitis, when it does occur in neonates, is usually severe [11], and thirdly, children should be immunised under cover of maternally acquired antibodies If this is done, there should be no objection to incorporating an adjuvant in the vaccine

THE FORTY NINTH STAR

AMONG the United States of America (to which she has been elected this year) Alaska is likely to remain a nonesuch The new State measures about 2000 miles between extremities with a population of less than a quarter of a million, or 1 person to 3 square miles Of these, 38,000 are "natives" (Indians, Aleuts, and Eskimoes) and the rest " white " (which includes a few Negroes) Many of the whites are members of the Armed Forces on duty, and of the rest some are summer migrants from Seattle and San Francisco Most of the population of all races live in scattered settlements on the coast or in the large river valleys A large part of the country is virtually uninhabited Some of the natives are still partially nomadic and live by the chase There is a railway up country to Fairbanks, but boat and light aeroplane are the usual means of travelling All these distinguish Alaska from the continental States, but the factor which gives it uniquity is its climate A quarter of the new State lies within the Arctic circle, and the rest is as cold as charity for at least five months of the year " Permafrost " is an ungainly word for the state of the ground which is frozen solid in summer as well as in winter a few feet below the surface, but it is a very awkward reality It makes the supply of water and disposal of sewage equally difficult When the surface layer thaws in the spring the water cannot seep away, and in summer most of the low country is a morass which breeds uncountable hordes of blood-thirsty insects Travel even for a few miles is never easy, and in spring and autumn it is sometimes impossible Quickly maturing crops such as lettuces grow luxuriantly in the summer, and there is some dairying and poultry-keeping

In face of these difficulties a brave attempt has been made to offer the benefits of modern medicine to Alaskans of all races [1] Legend had it that when the first Americans landed on these barren shores (the Russian sealers had preceded them by a hundred years) the Indians and Eskimoes enjoyed remarkably good health on a diet of fish and meat—often raw and flavoured with some wild herbs and berries They did not suffer from scurvy (as the whalers did) but sometimes died of starvation Nowadays most of the natives have developed a regrettable taste for crackers and doughnuts and live a life not much different from that of the immigrants The crude death-rates, however, still show a figure for natives about twice that for whites, and for maternal and infantile deaths the difference is even greater The death-rates for accidents and homicide are about twice those of the U S A as a whole, and for alcoholism about six times But, contrasting the figures for 1958 with those for 1950, the change is for the better in almost every instance The reduction of the death-rate from tuberculosis from 175 to 12 per 100,000 is an outstanding triumph Alaskan home life—especially in the winter—is conducive to cross-infection Tuberculosis seems to have been introduced by the whites, and the natives were extremely susceptible The number of hospital beds was quite insufficient, and the isolation of the communities often deferred diagnosis until it was too late Now chemotherapy, a special allocation of funds from federal and territorial sources, and a determination to succeed have had their reward As in more favoured lands there are empty beds in the tuberculosis hospitals

Other infectious diseases take their toll Enteric infections are common (as they are in the north of Europe) but do not seem to differ from those elsewhere [2] Epidemic influenza occurs from time to time It is a land where man lives close to his animals *Echinococcus granulosus* and *E multilocularis* occur together Rabies is endemic among wild animals, but human infections are rare The only disease which Alaska might claim as its own is a corneal scarring of unknown origin, which is a major affliction of the natives There is obviously work enough to keep the four public-health laboratories occupied, but poor communications limit their usefulness The distribution of scanty medical resources in a thinly populated country is a problem all the world over In Alaska there are Government hospitals run by the Public Health Service and the Fish and Wildlife Service There are community hospitals and hospitals run by religious bodies Of 163 doctors, 117 are in private practice and most of these are in the larger cities on the south coast In addition, the Armed Forces have their own medical service To the outsider it seems a muddle, and likely to be even more of a muddle in this period of transition to Statehood One of the successes of our reviled National Health Service has been in rationalising the use of our hospitals to provide the best service to the community without waste or overlapping of functions If our colleagues in Alaska will not

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8 Spigland I , Goldblum, N *Pediatrics* 1960, 25, 812
9 Medical Research Council report *Brit med J* 1956, ii, 454
10 Pagano, J S , Plotkin S A Kiprowski, H *Lancet*, 1960, i, 1224
11 Bates, T *Amer J Dis Child* 1955, 90, 189

1 *Publ Hlth Rep*, *Wash* 1960 75, 878
2 *ibid* p 913

regard the suggestion as too indelicate, we would think that some such overriding authority would be a great help in their proud and ambitious new State

RENAL SEQUELÆ OF EPIDEMIC HÆMORRHAGIC FEVER

DURING the Korean campaign some 2000 cases of epidemic hæmorrhagic fever (E H F) occurred among the United Nations' Forces The clinical features of this disease are now well established [1–11] Some renal involvement is so constant that the diagnosis is scarcely tenable in its absence Albuminuria is found early and is commonly followed by a fall of urinary specific gravity and the appearance of blood and casts In the more severe cases oliguria, anuria, and nitrogen retention develop, together usually with a period of hypotension After the acute phase abnormal elements rapidly clear from the urine, and prompt restoration of renal function is the rule, although in some patients impaired urinary concentrating power persists for many months The mortality of the disease is 3–5% [7]

In fatal cases the kidneys contain striking lesions [12–16] of essentially "lower-nephron nephrosis" type [17] A distinctive feature of the renal lesion is hæmorrhage in the junctional zone—an expression of the generalised capillary damage in E H F There is extensive necrosis of tubular epithelium with gross rupture of many tubules The nature of these lesions has been beautifully demonstrated by micro-dissection [18]

In view of the sometimes-severe renal damage it is perhaps surprising that in the majority of cases renal function is restored fairly rapidly Long-term follow-up of the widely dispersed survivors of this epidemic is difficult, but a survey of records and a limited clinical study have been carried out [19] The medical records of 1416 U S Servicemen who had E H F between January, 1951, and August, 1953, were examined The majority recovered clinically within a few weeks of onset, but in 25% urinary concentrating power was not restored for eight weeks, and in 9% this was impaired for twelve or more weeks The nature and frequency of subsequent hospital admissions (other than for follow-up) to the end of August, 1956, were analysed In this period disease of the urinary tract had been diagnosed in 35 of the E H F survivors—an incidence significantly greater than that among a suitable control series Pyelonephritis was frequently diagnosed, although bacteriological proof was rarely obtained The significance of these findings is uncertain, as a history of E H F may somewhat prejudice subsequent clinical judgment In 4 cases urinary concentration was impaired more than two years after the acute attack, and in 2 excretion of phenolsulphonphthalein was abnormal There was no evidence of renal failure or of progressive disease Hypertension was not encountered A clinical study of a partly selected group of 15 survivors of severe or moderate E H F yielded evidence of mild defects of renal function after intervals of up to four years, impairment of tubular function being greater than concomitant reduction of glomerular filtration These findings, which cannot be due to loss of complete nephron units, perhaps indicate imperfect regeneration of specialised tubular epithelium Continued improvement appears possible for several years

This work casts light on the residual renal damage after E H F and emphasises the essentially good prognosis for the majority of patients The few who do not recover completely suffer a minor loss of renal reserve probably compatible with normal duration of life Similar recovery of function is found after acute renal failure from other causes, although the initial mortality is much higher than in E H F [20 21] Whether residual damage resulting from this disease will predispose to the development of hypertension is still uncertain

CHINESE VIEW

REPRESENTING the Chinese Medical Association, six Chinese doctors have been spending a few weeks in this country at the invitation of the Royal College of Physicians of London As three of them work at the Chinese Academy of Medical Sciences in Peking, and two others hold chairs in Shanghai, their interest has been mainly in scientific developments, and outside the London area visits have been paid to Edinburgh, Glasgow, Oxford, Cambridge, Liverpool, and Newcastle

Having thus seen something of British research, especially in their own subjects, the delegation offered in return to give some account of developments in their own country, and on Dec 12 Dr Hsueh Kung-Chuo, vice-president of the Academy, gave a lecture at the London School of Hygiene and Tropical Medicine What he said about the control of epidemic diseases and the remarkable advance of public health was familiar to some of his hearers from the reports of Western doctors who have visited the People's Republic [22], but all must have been freshly impressed by his emphasis on the advantages of fusing Western and traditional methods of medicine—a policy which Communist leadership has increasingly urged on the Western-trained profession in China Mention was made of "combined" methods of treatment, including traditional methods such as acupuncture, cupping, and breathing exercises, which are said to have given good results in chronic conditions such as hypertension and diabetes, and of regimes by which the majority of patients with appendicitis, cholelithiasis, and other conditions can be spared operation On these matters we await further evidence with interest but with the cautious scepticism which is necessary for arriving at truth Continuing scientific advance depends on dispassionate weighing of evidence, and the Chinese have yet to show that this is compatible with political leadership Application of known facts is one thing but discovery of new ones is quite another

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Points of View

PER ARDUA AD ARDUA

D M McClure
M B Glasg

"The shades of night were falling fast,
as through an Alpine village passed
a youth who bore 'mid snow and ice,
a banner with the strange device
'Excelsior!'"

Scientific progress is the watchword of our times Not only does the momentum of our advance increase daily, but every fresh piece of recorded data is seen as a further step towards a clearly defined goal, the attainment of which is only a matter of time

This is best shown perhaps in the attitude of the layman to the "cure for cancer" There can be few of us who have not been asked "But surely doctor, it's bound to come, isn't it? I mean, look at the amount of work that is being done!" To which one might reply that certainly the amount of investigation is vastly greater than ever before, that the tools of research are of ever-increasing complexity and scope, and that in every medical library, the very walls are bulging with the growing masses of undigested and indigestible data

My present concern, however, is with more general considerations, and I shall comment on our failures to date in comprehending the vital processes of the cell (of which neoplasia is only one facet), and on the significance of the flood of medical literature which is overwhelming us all In doing so, I would justify my apparent temerity by pointing out that the climbers on the highest pinnacles of the mountain of knowledge can be best observed from a position on its lower slopes

* * *

In his first days as a student, the aspiring doctor is introduced to *Amœba proteus*, and is invited to philosophise on the imponderable mysteries of life locked away in this minute particle of protoplasm, as seen by "the eye which has a mind behind it" In later years, however, when we come to deal with countless millions of cells, enormously varied in structure and function, and linked in a dynamic equilibrium to form the living human body, there seems to be no limit to the degree to which we presume to comprehend the most fundamental of their vital functions

It is of course a basic human weakness, that we are unwilling to face any facts the recognition of which would be detrimental to our self-esteem, and we instinctively oppose any suggestion that there are limitations to the powers of the human intellect We have no illusions concerning our other physical capacities there are too many proofs in Nature of attributes superior to ours in muscular strength, acuity of eyesight, and so forth But man owes his ascendancy to his brain, and we are notably reluctant to admit any bounds to our capacities in this respect Today, however, we are having this recognition forced upon us

The limitations relevant to our subject are those of our perceptive faculties, and I need specify only two The first is our extremely limited power of instantaneous perception of number (readily shown by determining for how many black dots on a white card one can give the total number at a glance without individual enumeration), and the second is the fact that we have no sensory mechanism for appreciating, quantitatively, the interplay of forces maintaining an unstable equilibrium Our limited perception of number virtually ceases to exist when we are confronted with a group of similar units in constant random movement even the most mathematical of us cannot count a flock of sheep on the move, and the exasperated cry of "Stand still for a moment can't you!" is familiar to all who undertake the management of children For an illustration of my second point, one may observe that the feats of the equilibrist and juggler are the result of years of reflex conditioning, and that the control he exercises does not derive from any quantitative judgment of the bearings and intensities of the forces he manipulates

* * *

Before relating these points to the investigation of the living cell, one might profitably glance at events since the time of Virchow In the first three-quarters of the century which has elapsed, the improvement of the microscope, and of the techniques of tissue processing, sectioning, and staining, created the science of "classical" morbid histology The potentialities of this were so vast that years of continuous progress passed before any boundaries to them became apparent through developments in biochemistry and an increasing appreciation of cellular dynamics By that time, a picture of disease processes in terms of hæmatoxylin and eosin was no longer enough In microscopy, too, optical limitations had become increasingly obtrusive, nor were these adequately overcome by ventures into the ultraviolet There was thus a general frustration, with the conviction that the most vital information lay just beyond the utmost limits then available of magnification and resolution

Since then, however, the whole picture has changed, and a host of new developments in instrumentation has been showered on us—phase contrast, electrophoresis, chromatography, freeze drying, spectrophotometry, radioisotopes, the ultracentrifuge, interference microscopy and, most spectacular of all, the electron microscope One might well suppose that, with these formidable reinforcements, the remaining obstacles could be swept aside with ease, and that final unders[illegible]ding was at last within our grasp, but the resul[illegible] [illegible]ate suggest that this i[illegible] hardly so

Let us consider for a m[illegible] t some r[illegible]
electron microscopy of bi[illegible]
larly t[illegible] verbal pr[illegible]
the stu[illegible] blood p[illegible]
typical

"The[illegible]
membra[illegible]
they ma[illegible]
artifact"

"Th[illegible]
of the firs[illegible]

Or in the[illegible]

"Fine d[illegible]
backgroun[illegible]
bar shape[illegible]
are of ir[illegible]
densities"

And let us[illegible]

"Two va[illegible]

1
2
3 R

"a remarkable structure somewhat reminiscent of vertebræ" "A fibrillar sheath which may or may not be spiral"

It would, one feels, be something of an overstatement to describe any of these observations as a blinding revelation of ultimate truth, and in the similar application of phase contrast[4] the same descriptive terms abound

"Angular blocks of heterochromatin" "Highly refractile specific granules" "Large dark ellipsoid mitochondria"

In every instance we are dealing with verbal renderings of visual impressions of structural entities, whose functional significance cannot be assessed by any process of inspection, and, even where an attempt is made to study an active vital process, as in bacterial cell division,[5] we read that "the impression is gained that before actual division, there are deep lying processes going on, for the bacteria become suddenly restless, and have continuous changes of form"—a description which certainly conveys the sense of activity but tells us nothing of the mechanisms involved.

Indeed, so far from bringing us nearer to complete understanding of cellular function, these advances in microscopy seem to emphasise the presence of barriers to our further comprehension, by revealing structural complexities and minutiæ whose role cannot be interpreted by visual inspection. This, however, is hardly surprising, since the ultimate goal of our search lies in a dynamic equilibrium of the utmost complexity, maintained by an interplay of forces whose analysis is beyond the scope of our sensory receptors. One has only to glance at a living leucocyte by phase contrast to appreciate the self-deception in which we indulge by our descriptions of the shrunken and artificially pigmented remains of similar cells—a deception which we foster by the titles and eponyms which have so long served to cloak our ignorance. One can imagine an attempt to describe in similar phraseology the components of a watch, by someone with no knowledge of their purpose: the main and hair springs might be termed the "greater and lesser spiral filaments", the jewels the "rubroid bodies", and the regulator could well become "the digitate organ of Pflugelheimer"!

In trying to interpret the functional roles of intracellular particles by observing the living cell, the position of the microscopist can be likened to that of a man from Mars in his flying saucer, viewing a series of football matches. This comparison is by no means too fanciful, if one considers such a viewpoint in cytological terms:

> An ovoid area, with a broad peripheral zone of densely packed identical particles exhibiting a trace of Brownian movement, and throughout which radial striations appear with varying degrees of clarity. Within this there is a clear central area, in which a strikingly constant linear pattern is displayed, and throughout which a small number of particulate bodies show active and apparently random motility. Well-defined chromatic differentiation is commonly shown by these, though this is not invariable and continued observation shows a frequent tendency for these bodies to form temporary aggregates at one or other polar extremity of this central area. Certain observers have reported the presence in this zone of a much smaller single particle moving at very high speeds, and further confirmation of this point is awaited.

It is on the whole rather doubtful whether our Martian observer will, in time, be able to interpret the niceties of the offside rule, and I suggest that our own view of the living cell is equally disadvantageous in respect of the visual interpretation of functional activities.

* * *

At this stage then, one is compelled to admit that to see is not necessarily to comprehend, and our hopes that these new techniques would provide the answers have not been realised. There is, too, a further fallacy in our approach to the relationship of cellular structure and function. In dealing with the whole organism, we are able to consider organs and systems as separate entities, and thus we can study the heart and circulation without any direct correlation with, for example, gastrointestinal function, but when we consider any individual intracellular body we find ourselves in a realm where the function of any single component can only be expressed by its dynamic relationship in terms of molecular equilibrium with each and every other constituent entity of the cellular protoplasm. It is this fact which confronts us squarely with those fundamental limitations in our powers of perception and comprehension to which I have already referred. Nor does it avail us to invoke the aid of chemistry, for we have already reached the point at which chemistry and physics lose the last trace of any separate identity, and beyond which we have to discard the alphabetical symbols by which we are accustomed to represent molecular structure. The human intellect cannot bridge the gap between the representation of chemical structure by arbitrary symbols, and the comprehension of the reality of matter in dynamic terms of fundamental particles, nor are we much aided in this by molecular models of coloured plastic balls. These are still static symbols, and the essential fact which we so readily forget is that each individual chemical atomic symbol represents in itself a dynamic entity of particles whose true nature is unknown to us, involving as they do the ultimate mystery of the "emptiness" of matter. The position becomes ludicrous when we use such symbols to build up a structural picture with spatial relationships so complex that we cannot retain a coherent mental picture of them—as in our diagrams and models of the molecular structure of aminoacids and proteins. In our preoccupation with the configuration of such molecules, we forget that the basis of vital activity lies not in patterns of spatial relationships but in the forces which maintain or alter these relationships, and when we view the living cell, we are all too ready to regard the activity of the protoplasmic particles as a hindrance to detailed study, whereas it is in the balance of these forces that the ultimate truth resides.

You may wish to remind me that in enzyme chemistry, serology, and histochemistry there is a large body of workers whose efforts are also directed to matters of vital dynamics, and I hasten to acknowledge my awareness of their activities. But they too suffer in the pitfalls of attempting to equate dynamic processes with static symbols. In the nevernever land where every factor has a co-factor, every enzyme a co-enzyme, every active principle an inactive precursor, and all are surrounded by potentiators, inhibitors, and accelerators lavishly endowed with stable and labile fractions, nothing is quite so elusive as the factor which "has still to be isolated in a pure form". It may be pertinent to comment that one may observe and measure the resultant of a complex of forces, but that this resultant cannot exist independently of the forces which give rise to it. Again, the problems which beset these workers have some affinity with those of a child attempting to pick up a globule of mercury: it keeps on dividing into smaller globules of varying size which can be reconstituted into the original one, and, moreover, the number and size of these fractions is not constant from one attempt to the next. This may well have some bearing on the familiar type of statement to the effect that "the co-factor R, hitherto regarded as identical with the sub-fraction XI, has now been shown to differ in the possession of a thermolabile constituent associated with the α_2-globulin." All of which simply emphasises the fact that in dealing with entities for which the conventional symbols of chemistry are invalid, the substitution of arbitrary titles for a variety of intangibles solves nothing, and one might pose the question: "Given any two points A and B on a linear graph, how many intermediate points can be plotted?"

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[4] Discombe G *Acta haemat* 1950 3 151 (Abs in Year Book of Pathology and Clinical Pathology Chicago 1950)

[5] Hassmann H Kappel W *Arch Derm Syph Wien* 1949 187 501 Abs Year Book of Pathology and Clinical Pathology Chicago 1949

It follows therefore that any understanding of these matters must be sought not in symbols of chemistry but of mathematics—in which we must include the fourth dimension of time. The problem here is that we cannot begin to look for it without quantitative physical data on the fundamental particles of matter participating in cellular function, yet when we venture to derive such data from living protoplasm, we find ourselves without any fixed point of reference to which we may relate our measurements. Furthermore, when a single molecule of protein can involve complexities exceeding our faculties of comprehension, how do we presume to proceed to the full understanding of the complex of forces binding the millions of molecules in the cell, and thereafter to the balance of forces throughout the millions of such cells in the whole organism?

The answer is, I fear, that we cannot. In considering an entity of almost infinitely complex relationships, the simultaneous comprehension of the whole and the relationship of each constituent part to every other is not within the capacity of the human mind. And one of the principal causes of the current deluge of medical and allied scientific literature is the fact that when the biological investigator reaches the point of being unable to see the wood for the trees, he is all too ready to attempt to resolve his difficulties by embarking on the study of individual leaves!

* * *

Having made this point then, I must offer an answer to the question implied in my opening paragraph. Is it true that, in our scientific "progress", we are moving steadily towards an attainable goal, and, if not, what is the significance of the ever-increasing activity in research? The answer to the first part is an unequivocal "No", and the reason lies in the answer to the second part. As a first step to providing this, I would quote an analogy from Florey's *General Pathology*.[6] In referring to the difficulties of interpreting functional disorder from tissue sections, he comments: "It is as if a full length cinema film were taken, every two hundredth frame extracted, the extracted frames jumbled together, and an observer was then asked to reconstruct the story of the film from them." By a simple extension this analogy can provide a comprehensive and convincing answer to our question.

Let us consider the course of events if, instead of seeing a new film in the normal way, every press critic were presented with the full thousand yards or so of celluloid strip, with a hand lens, and were instructed to extract the maximum amount of information from its study, frame by frame, and in doing so, to compare notes regularly with all the others similarly engaged. It would be immediately apparent whether the film was in a modern or a "period" setting, or whether it dealt with Naval warfare, "Western" adventure, or "Big City" life. On these preliminaries, there would be uniform agreement. The next step however, would be to identify the actors, and here disagreement would soon be apparent—even concerning the stars.

That however is only a beginning. Next there would be the evaluation of the plot and characters of the film, and here the observers would enter a realm of pure speculation. Certain identifying features would of course appear at times, but usually the inspection of consecutive frames would give little insight into the human relationships being depicted. Nevertheless, our observers would evolve various hypotheses based on their scrutiny, and argument would revolve around these. At a later stage, occasional facets of detail would be picked out which would compel the abandonment of views which had been generally accepted.

"The observation by Snooks (1959) that the Vauxhall car in frames 6026 to 6618 is a 1954 model, and not a 1953 model, reopens the question of the identity of its driver, as A. B. the actor believed to have taken this part died in March of the latter year."

And so it would go—the scope for speculation and argument would expand continually, with the scrutiny of ever more minute features of detail—even to the point whether the date on the second tombstone on the left was 1864 or 1866. And of course, special investigations might rear their heads. "A review by model, date, and registration number of cars and motorcycles appearing in street scenes", by Tweedledum A. and Tweedledee B. (A.A. and R.A.C. research scholars), might well be followed by "A critical evaluation of certain anomalies and discrepancies in continuity, with special reference to anachronisms." The extraction of factual data would be virtually endless, but, even when every scrap of the information thus acquired had been assembled, two vital points would remain unanswered and unanswerable—the quality of the acting performances, and the entertainment value of the film!

* * *

And now perhaps the application of the analogy to the current mass of medical publication is clear—namely, that the vast majority of all articles and studies on cellular function are similarly devoted to the minutiæ of static and background detail, wholly divorced from the dynamics of life itself. Our general failure to appreciate this derives, I suggest, from the fact that whereas in the film analogy the successive frames represent only two-dimensional images of three-dimensional subjects, our biological specimens are three-dimensional entities, accessible to laboratory processes. What we overlook is that in taking our samples we are removing them from their proper context of vital activity in both space and time, and that the steps to which we subject them correspond to cutting out the film-strip figures with scissors, or to scraping off the emulsion, as a preliminary to closer individual scrutiny. (When a writer on cellular respiration[7] refers to "properly isolated mitochondria" one is not altogether clear as to the precise criteria of propriety in this matter, but presumably they approximate to those applicable to a properly eviscerated viscus!) There is, too, a further point on which we would do well to ponder namely, that, so far as our senses are concerned, the only way in which the particles of cellular protoplasm can impinge on these is as retinal stimuli We stand in the same relationship to these particles as does the astronomer to the uttermost stars, and at either extreme we see through a glass darkly

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[6] Florey, H. W. General Pathology, p. 10. London, 1958.

[7] Glazer, A. N. *Advanc. Sci. Lond.* 1956, **12**, 398.

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What conclusions may one presume to offer? In the first place, I think we should emphasise the distinction between the accumulation of data and the advancement of knowledge The assimilation of a mass of information is a process which can only be carried out by the individual, and his capacities are limited not merely by considerations of intellect but also by the need to spend part of each twenty-four hours in sleep, and ultimately by the span of life itself One does not need to be a Montgomery to appreciate that, in a military campaign, advance without consolidation spells ultimate disaster from breakdown in the lines of communication, and in medical science the point at which the breaking strain is developing is in the impossible task of incorporating the essentials of a growing mass of increasingly specialised knowledge in the basic education of the student Indeed, the position of the student today—which includes us all—resembles that of a solitary diner confronted with the products of a thousand chefs, all simultaneously engaged in producing a continuous succession of culinary masterpieces!

Quite apart from the sheer quantity of information, there is the even more important matter that, in our zeal for continuous advance on every front, we are failing to give adequate thought to our ultimate aims If one were to pose the question as to what in fact is our ultimate goal, the general answer would undoubtedly be "the conquest of disease" Having made this reply, however, few will trouble to think further about the practical implications of their statement (which is widely used indeed the claim is often made that certain diseases have already been overcome) To do so, we must first define the most fundamental duty of the doctor If, again, the public were invited to specify this, the majority would almost certainly give it as "the preservation of human life" and in this, surely, lies a basic error

One recognises of course that current emphasis is directed to "positive health" rather than to awaiting the appearance of disease, and this is eminently proper during that greater part of the normal lifetime in which the attainment of health is a practical possibility Ultimately, however, the doctor encounters circumstances—terminal carcinomatosis, senility with bedsores and incontinence, and other comparable states—in which not only has the attainability of "positive health" vanished for ever but the preservation of life itself is equally impossible But he still has his most fundamental duty which is the relief of suffering, in which his obligations are not discharged until life is extinct In our constant probing into the cell, therefore, we must bear in mind that however vast an array of established fact we acquire, this knowledge will never ensure the perpetual continuity of function of any living organism, and it should be clear that our much-vaunted goal of the 'conquest of disease" calls for some more searching analysis

A fact to which we are all too ready to turn a blind eye is the ultimate inevitablity of death, and in practice we reach a point where our efforts to overcome disease merge into a futile attempt to postpone death in circumstances where its physical processes are irreversibly established It is true of course that, in the life of any individual, medical intervention may avert repeated dangers, any one of which could have been fatal, but there is no such thing as the conquest of disease The position is directly comparable to the efforts of the Dutch in keeping the sea at bay Their dykes are erected, strengthened, and extended Now and again a collapse occurs, with inroads of flooding, in response to which resources are marshalled and the breach is repaired, but continued safety is achieved only by constant vigilance and structural maintenance The ocean is always there, and there is no end to the processes of gradual erosion and the searching out of weak points in the defences, nor is time of any account to the sea The same is true of disease in all its aspects There is no escape from the fundamental truth that we must all die, and that some will die sooner than others This is an unalterable fact Were it otherwise, we would have to contemplate a situation in which the human body would attain a state paralleling that of the "wonderful one-hoss shay" of Oliver Wendell Holmes, in which, as you will recall, the structural materials were of such superlative excellence that no single component wore out before another, so that in the final issue there was no localised mechanical breakdown, but a single synchronous cataclysmic collapse of everything No-one could regard this as an attainable, or even a desirable, ideal, and one might ask whether, in many of our efforts to lessen man's vulnerability, we are not engaging in a vain attempt to deny his mortality—the more so at the present time, as a glance at the standard tables of life expectancy will show that our current average is approaching the Biblical limit of three score and ten, a circumstance in which the linear graph of the effort and cost per unit of further progress describes a curve which is now climbing almost vertically

* * *

At this point the reader who has borne with me thus far may wish to pose a final question "If I am suggesting that in our efforts to comprehend the living cell, most of our activities amount to beating our heads against a brick wall while uttering happy cries, how do I reconcile this with the undeniable fact of the enormous and increasing expansion of every branch of science?"

I have already exceeded my quota of analogies, but to answer this, I ask indulgence for one more If we can picture the individual molecules of a soap bubble as sentient entities, then we have this situation While the bubble is being blown, they would be aware of two factors first, a gradual movement radially, steadily increasing their distance from the centre of the sphere, and secondly an increasing peripheral tension between them and their immediately contiguous neighbours at all points —a force imposing a progressive limitation on their range of local movement At the bursting of the bubble, however, and in the microseconds immediately thereafter, the first impact of the event on their consciousness could only be by their awareness of a tremendous surge of acceleration upwards and outwards, far exceeding anything in their previous experience, and coupled with a sudden release from the restrictive peripheral tension to which they had previously been subjected

With this in mind then, let us extend our time-scale of microseconds to decades, and substitute for the image of the bursting bubble the pattern of events in medical of a child attempting to pick up a globule of mercury it keeps on dividing into smaller globules of varying size which can be reconstituted into the original one, and, moreover, the number and size of these fractions is not constant from one attempt to the next This may well have some bearing on the familiar type of statement to the effect that "the co-factor R, hitherto regarded as identical with the sub-fraction XI, has now been shown to differ in the possession of a thermolabile constituent associated with the α_2-globulin" All of which simply emphasises the fact that in dealing with entities for which the conventional symbols of chemistry are invalid, the substitution of arbitrary titles for a variety of intangibles solves nothing, and one might pose the question "Given any two points A and B on a linear graph, how many intermediate points can be plotted?"

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And so it would go—the scope for speculation and argument would expand continually, with the scrutiny of ever more minute features of detail—even to the point whether the date on the second tombstone on the left was 1864 or 1866 And of course, special investigations might rear their heads "A review by model, date, and registration number of cars and motorcycles appearing in street scenes", by Tweedledum A and Tweedledee B (A A and R A C research scholars), might well be followed by "A critical evaluation of certain anomalies and discrepancies in continuity, with special reference to anachronisms" The extraction of factual data would be virtually endless, but, even when every scrap of the information thus acquired had been assembled, two vital points would remain unanswered and unanswerable—the quality of the acting performances, and the entertainment value of the film!

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And now perhaps the application of the analogy to the current mass of medical publication is clear—namely, that the vast majority of all articles and studies on cellular function are similarly devoted to the minutiæ of static and background detail, wholly divorced from the dynamics of life itself Our general failure to appreciate this derives, I suggest, from the fact that whereas in the film analogy the successive frames represent only two-dimensional images of three-dimensional subjects, our biological specimens are three-dimensional entities, accessible to laboratory processes What we overlook is that in taking our samples we are removing them from their proper context of vital activity in both space and time, and that the steps to which we subject them correspond to cutting out the film-strip figures with scissors, or to scraping off the emulsion, as a preliminary to closer individual scrutiny (When a writer on cellular respiration[7] refers to "properly isolated mitochondria" one is not altogether clear as to the precise criteria of propriety in this matter, but presumably they approximate to those applicable to a properly eviscerated viscus!) There is, too, a further point on which we would do well to ponder namely, that, so far as our senses are concerned, the only way in which the particles of cellular protoplasm can impinge on these is as retinal stimuli We stand in the same relationship to these particles as does the astronomer to the uttermost stars, and at either extreme we see through a glass darkly

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[6] Florey, H W General Pathology, p 10 London, 1958

[7] Glazer A N *Advanc Sci Lond* 1956, 12, 398

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What conclusions may one presume to offer? In the first place, I think we should emphasise the distinction between the accumulation of data and the advancement of knowledge The assimilation of a mass of information is a process which can only be carried out by the individual, and his capacities are limited not merely by considerations of intellect but also by the need to spend part of each twenty-four hours in sleep, and ultimately by the span of life itself One does not need to be a Montgomery to appreciate that, in a military campaign, advance without consolidation spells ultimate disaster from breakdown in the lines of communication, and in medical science the point at which the breaking strain is developing is in the impossible task of incorporating the essentials of a growing mass of increasingly specialised knowledge in the basic education of the student Indeed, the position of the student today—which includes us all—resembles that of a solitary diner confronted with the products of a thousand chefs, all simultaneously engaged in producing a continuous succession of culinary masterpieces!

Quite apart from the sheer quantity of information, there is the even more important matter that, in our zeal for continuous advance on every front, we are failing to give adequate thought to our ultimate aims If one were to pose the question as to what in fact is our ultimate goal, the general answer would undoubtedly be " the conquest of disease " Having made this reply, however, few will trouble to think further about the practical implications of their statement (which is widely used indeed the claim is often made that certain diseases have already been overcome) To do so, we must first define the most fundamental duty of the doctor If, again, the public were invited to specify this, the majority would almost certainly give it as " the preservation of human life " and in this, surely, lies a basic error

One recognises of course that current emphasis is directed to " positive health " rather than to awaiting the appearance of disease, and this is eminently proper during that greater part of the normal lifetime in which the attainment of health is a practical possibility Ultimately, however, the doctor encounters circumstances—terminal carcinomatosis, senility with bedsores and incontinence, and other comparable states—in which not only has the attainability of " positive health " vanished for ever but the preservation of life itself is equally impossible But he still has his most fundamental duty which is the relief of suffering, in which his obligations are not discharged until life is extinct In our constant probing into the cell, therefore, we must bear in mind that however vast an array of established fact we acquire, this knowledge will never ensure the perpetual continuity of function of any living organism, and it should be clear that our much-vaunted goal of the " conquest of disease " calls for some more searching analysis

A fact to which we are all too ready to turn a blind eye is the ultimate inevitability of death, and in practice we reach a point where our efforts to overcome disease merge into a futile attempt to postpone death in circumstances where its physical processes are irreversibly established It is true of course that, in the life of any individual, medical intervention may avert repeated dangers, any one of which could have been fatal, but there is no such thing as the conquest of disease The position is directly comparable to the efforts of the Dutch in keeping the sea at bay Their dykes are erected, strengthened, and extended Now and again a collapse occurs, with inroads of flooding, in response to which resources are marshalled and the breach is repaired, but continued safety is achieved only by constant vigilance and structural maintenance The ocean is always there, and there is no end to the processes of gradual erosion and the searching out of weak points in the defences, nor is time of any account to the sea The same is true of disease in all its aspects There is no escape from the fundamental truth that we must all die, and that some will die sooner than others This is an unalterable fact Were it otherwise, we would have to contemplate a situation in which the human body would attain a state paralleling that of the " wonderful one-hoss shay " of Oliver Wendell Holmes, in which, as you will recall, the structural materials were of such superlative excellence that no single component wore out before another, so that in the final issue there was no localised mechanical breakdown, but a single synchronous cataclysmic collapse of everything No-one could regard this as an attainable, or even a desirable, ideal, and one might ask whether, in many of our efforts to lessen man's vulnerability, we are not engaging in a vain attempt to deny his mortality—the more so at the present time, as a glance at the standard tables of life expectancy will show that our current average is approaching the Biblical limit of three score and ten, a circumstance in which the linear graph of the effort and cost per unit of further progress describes a curve which is now climbing almost vertically

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At this point the reader who has borne with me thus far may wish to pose a final question " If I am suggesting that in our efforts to comprehend the living cell, most of our activities amount to beating our heads against a brick wall while uttering happy cries, how do I reconcile this with the undeniable fact of the enormous and increasing expansion of every branch of science?"

I have already exceeded my quota of analogies, but to answer this, I ask indulgence for one more If we can picture the individual molecules of a soap bubble as sentient entities, then we have this situation While the bubble is being blown, they would be aware of two factors first, a gradual movement radially, steadily increasing their distance from the centre of the sphere, and secondly an increasing peripheral tension between them and their immediately contiguous neighbours at all points —a force imposing a progressive limitation on their range of local movement At the bursting of the bubble, however, and in the microseconds immediately thereafter, the first impact of the event on their consciousness could only be by their awareness of a tremendous surge of acceleration upwards and outwards, far exceeding anything in their previous experience, and coupled with a sudden release from the restrictive peripheral tension to which they had previously been subjected

With this in mind then, let us extend our time-scale of microseconds to decades, and substitute for the image of the bursting bubble the pattern of events in medical science in the present century. The parallel must, I feel, be clear, but for added emphasis, it can readily be developed. The next stage as the pattern unfolds is that of our initial exhilaration becoming progressively tempered by the consciousness that the Science of Medicine is no longer a coherent and unified structure, but a series of isolated bodies without intercommunication or co-ordination, which are becoming more and more widely separated, and then by the increasingly disquieting realisation that in our own particular unit, while our speed continues undiminished, not only do we have no effective control over its degree or direction, but there is no sign of any ultimate point of arrival.

In the midst of all that we choose to call progress, therefore, it might repay us to reflect that there is no such thing in Nature as a structure—material or social—which is capable of perpetual expansion, and in the advancement of knowledge the ultimate limiting factor is the fact that in each succeeding generation the newborn infant arrives without any legacy of the accumulated knowledge and experience of its parents. Before the summits attained by the latter can be surpassed, the ascent must be repeated by their successors.

* * *

As to the future, I have already presumed too much in the role of prophet, but I would venture one comment. I began by referring to the general attitude towards the "cure for cancer", which of course is only one facet of the ever-increasing demand for miracle drugs". Surveying the contemporary scene, one cannot but feel that instead of relying on an endless flow of polysyllabic organic pharmaceuticals, we should be better equipped for the years ahead by a philosophy of life which would enable us to recognise and accept our limited tenure of existence, and in doing so, to face its end with dignity and courage. This was not lacking in bygone generations, and, as the progress of Nature tends to move in cycles, we may, in time, find ourselves guided towards its rediscovery.

Conference

ACCIDENT SURGERY

A CONFERENCE on accident surgery was held in the Royal Faculty of Physicians and Surgeons of Glasgow on Nov. 30 to Dec. 2.

Causes and Treatment

Mr WILLIAM GISSANE said that the usual cause of injury, very rapid deceleration, had been studied in the United States Air Force on jet-propelled sledges which were decelerated from 150 to 34 m.p.h. per hour in $^{1}/_{4}$ second, which produced a force of 46.2*g* and 8000 lb. load on the harness.

If such a force was not to be fatal, it had to be applied over a wide area and not too rapidly. Safety-straps must include the shoulders, especially for front-seat passengers. The accident-rate per 1000 vehicles on the road was falling, but the total accident-rate was rising steadily and would reach 500,000 injuries per year in the near future. Mr Gissane compared the administrative cost of motor insurance (£23 million) with the cost of treatment (£11 million), figures that indicated a false sense of values. He made a plea for the segregation of slow-moving traffic from fast vehicles.

Mr WILLIAM SILLAR described the chest injury as a challenge to modern surgeons which had not yet been adequately answered. The points which told against the patient with chest injury included obstructed airway, hæmorrhage, sucking wound, tension pneumothorax, tamponade, mediastinal emphysema, and paradoxical movement. Mr Sillar was disappointed by the patient-triggered respirator: an intermittent positive-pressure respirator was proving better. He advocated fusion of the chest segment, either by traction with 'Cellophane'-covered flex or by fixation by a Kirschner wire. Anterior-segment injuries were the most severe, and some of them could be dealt with by plating of the sternum.

Discussing the management of the unconscious patient Mr JOSEPH SCHORSTEIN pointed out that unconsciousness varied from slight concussion to antemortem coma. Even slight cerebral œdema might lead to increased intracranial pressure and eventually to coning through the tentorium. A comatose patient should not be nursed on his back, but with the foot of the bed elevated. The mouth and pharynx should be aspirated frequently, and physiotherapy used to prevent chest complications. It might be possible to deal with respiratory obstruction by endotracheal tube, but only for 24 hours. The indications for tracheostomy were failure of pharyngeal suction, injuries and infections of the chest, and other injuries which prevented frequent change of position.

Reactions to Injury

Speaking of the metabolic reaction to injury, Prof THOMAS SYMINGTON said that "traumatic inflammation" was now recognised as an endocrine response of the pituitary-adrenal axis, and he described the post-traumatic response of the adrenal and the secretion of steroid hormones. Aldosterone was also produced in shock. The negative nitrogen and potassium balance found after injury might be due to starvation, low intake of water, or immobility. In fat-embolism there might also be an endocrine factor, a fat-liberating hormone.

Reviewing the biochemical problem of traumatic oliguria, Dr J. W. CHAMBERS stated that oliguria was a normal reaction to injury and the urine output might fall to 500 ml. per day. When severe oliguria developed, it was usually associated with tubular necrosis. Post-traumatic kidney change was often associated with severe and prolonged oliguria. Hypotension might be the only cause of the kidney change, but toxæmia was also involved in injury during pregnancy. Pure toxic effects were seen in carbon-tetrachloride and mercuric-chloride poisoning. The symptoms of acute renal failure included anorexia, nausea and vomiting, diarrhœa, drowsiness and restlessness, tachycardia, hypertension, leucocytosis, anæmia, tendency to bleed, and defects of healing. The condition might be avoided by planned and adequate transfusion or by correction of depletions.

Dr A. C. KENNEDY divided the treatment of acute renal failure into prophylaxis, conservative management, treatment in the diuretic phase, and use of the artificial kidney. Prophylaxis was summed up in the control of hæmorrhage, the restoration of blood-volume and blood-pressure, the prompt removal of damaged tissues, and the control of infection. Rational conservative therapy was introduced by Bull and others, and in modern modifications of the regimen the daily volume of fluid was 400 ml. Carbohydrate was now given to spare 50% of protein breakdown—about 100 g. per day.

Burns

Mr IAN MCGREGOR divided the damage in the acute phase of burns into skin damage and capillary damage. There were three degrees of capillary damage: capillary leak, stasis and hæmoconcentration (this stage was irreversible and necrosis would follow), and coagulation. Erythrocytes were always injured, and hæmoglobinuria might be produced. In a 50% burn, 12% of the red cells might be destroyed. The capillary leak was greatest in the first 8 hours and ceased at 48 hours Replacement should also follow this rate of flow In general, a burn of the adult below 15% and of the child below 10% did not require transfusion, but prevention of shock was better than treatment Mr McGregor preferred plasma as transfusion fluid, though occasionally whole blood was required for the extensive deep burn, after hæmoconcentration had been corrected, or electrolytes when oral intake was insufficient There was no satisfactory dose formula, and the clinical state should control dosage The first two pints could be given rapidly The clinical criteria were pulse-rate, packed-cell volume, peripheral circulation, thirst, and urine output (50 ml per hour in the adult)

Shock should be corrected before treating the burn Cleansing should be by detergent (e g , 1% cetrimide) and blister skin should be removed The method which most efficiently kept the burn dry should be used, so that dressing might be needed for one site and exposure for another (the hand should be dressed and the face and perineum exposed) The actual dressing was not important but should be adequate in extent and depth, and it needed fixation

Speaking on the late phase of burns Mr THOMAS GIBSON said this phase only arose in deep burns The problems were infection, protein loss, and anæmia ,all were aggravated by a raw area and grafting solved them, but these factors did not favour skin grafts The burn slough could be treated by immediate or delayed excision, or be allowed to separate spontaneously Excision should go down to deep fascia Delayed excision might start hæmorrhage Spontaneous separation took more than three weeks The infecting organisms were the streptococcus, which killed grafts, *Pseudomonas pyocanea*, which produced a toxin, and the staphylococcus, which was becoming more important in burns Protein loss might be partially prevented by gastric-tube feeding with protein or by intravenous albumin or plasma Homografts from mother or from brothers or sisters to the patient did better than from the father, but the advantage of long survival must be balanced against the disadvantages Cadaver skin might be used when it becomes legal to do so

Traumatic Ischæmia

Mr GEORGE SMITH said that ischæmia of muscle might be seen early after an injury but was recoverable up to 12 hours Later colliquative necrosis ensued, and little good could result from attempts to restore the blood-supply Early exploration was justified, and repair might be by end-to-end suture, by lateral arteriorrhaphy, or by grafting Vein grafts were favoured for small vessels and 'Teflon' for prostheses

Head Injuries

Mr G F ROWBOTHAM said that the indications for operation in head injuries might be early (immediate or within 48 hours), intermediate (2–28 days), or late (after 28 days) Early indications were anoxia, shock, loss of blood, compression of the brain, and compounding Intermediate operation was indicated by infection, increased intracranial pressure, and irritation Late operation was undertaken for chronic signs of head injury, epilepsy, bone defects, aneurysm, or nerve palsy Cerebral anoxia (possibly due to chest injury or inhaled vomitus) must first be treated Diagnosis should then be attempted and physiological therapy undertaken—replacing blood-loss, adjusting fluid and electrolyte balance, and ensuring adequate nutrition If surgery was required, definitive surgery should be done at the first operation

Visceral Injuries

Prof W A MACKEY said that visceral injuries were hard to classify because of coexistent lesions The liver was the organ most commonly damaged, then the spleen and the kidney The danger of damage to solid viscera was hæmorrhage, to hollow viscera, infection Treatment should include restoration of the airway and pulmonary function, control of hæmorrhage, stabilisation of major fractures, and closure of alimenatary defects A large incision was necessary Ileus should be treated by intragastric Levine tube and intravenous fluids to control the electrolytes

Orthopædic Problems

Mr E A NICOLL, in an account of fractures of the upper tibia, dealt first with the cause, prevention, and treatment of stiffness of the knee The cause was often œdema and no unnecessary immobilisation should be allowed Fracture of the tibial plateau might be difficult if the paracondyle gutters were affected, but the collateral ligaments were rarely involved and united readily, the classical plateau fracture depended on intact ligaments, instability being due to loss of the plateau and not to ligament injury Fracture of the tibial spine was an avulsion fracture and should be reduced Mr Nicoll described the treatment of stiffness, avoiding passive movement and movement against resistance until the last stage If there was no improvement for three months, quadricepsplasty was advised, loosening the adherent rectus femoris, cutting paracondylar and intra-articular adhesions, and correcting the shortened rectus In 17 cases described, improvement had ranged from 30° to 100°

Prof ROLAND EARNES discussed fractures of the cervical spine The commonest sites of injury were at the upper and lower ends, cord injuries being commonest at C5, 6, and 7 The mechanism of injury might be compression, flexion and rotation, or hyperextension Proprioceptive sensation was sometimes still preserved when the sensory functions were lost, and this was a good prognostic sign Treatment should be skull traction in the axis of the cervical spine, using Cone's callipers When the facets were clear, traction was reduced from about 30 lb to 5 lb and the spines were fused by a cancellous graft Laminectomy or removal of the articular facet was sometimes necessary Hyperextension injury was usually found in the old It was due to bulging of the interlaminar ligaments and produced a similar lesion to that of a prolapsed disc Treatment was rest in bed, avoiding extension

In the clean incised wound with section of the nerve, Mr ARTHOL PARKES favoured primary suture, avoiding axial disorientation He thought that muscle changes were minimised by early suture and that fibrosis might be reduced In the closed nerve injury, a waiting policy was probably justified, but nerve regeneration took a long time

Accident Services

Mr ROBERT WRIGHT thought that our present accident service was poor and outlined the requirements of a good service The main accident centres should be few and should have access to a specialist panel The smaller hospitals might receive patients back from the main centre for nursing after definitive treatment had been completed Staffing should be adequate to allow rest periods and refresher courses An orthopædic surgeon would be required but would not necessarily be in charge Training of students and general practitioners was required, but no doctor under the rank of senior house-officer should be on the staff of an accident centre Registrars from general surgery should spend six months of their training in an accident post A career accident surgeon should train in all the specialties

Dr CYRIL BAINBRIDGE, *senior administrative medical* officer of the Western Regional Hospital Board, noted the rise in outpatient attendance, many of them accidents The cost of the National Health Service in Scotland had risen from £26 million in 1949 to £52 million in 1959, and the community was entitled to expect better casualty services than it got There should be fewer but better accident centres, though local opposition could be expected to the closure of small units Probably one good accident centre was needed for each 200,000 population, it should have a burns unit, directed by a traumatic surgeon

Very Special Articles

NORMALCY AND THE GAMMA EFFERENT SYSTEM

JOHN H MENKES
M D John Hopkins

" No judgment can rightly be formed either of my method or of the discoveries to which it leads " —F BACON, *Novum Organum*

THE social, political, and economic upheavals of the past two decades have been a great strain upon the central nervous system of man, and upon its ability to adapt to the daily stresses to which it is subjected [1]

Recent experiments demonstrating that only the normal organism is capable of withstanding the slings and arrows of outrageous fortune [2] have placed a premium upon the normal man, and have led to attempts at defining the variables that circumscribe such a biological system

That a neurophysiological viewpoint might help with this vital problem was already postulated by Freud, who early in his career predicted that at some future time physiological data and concepts would be substituted for psychological ones *Es ist doch Alles Eins !*, he is said to have remarked after the famous Kitzbuhel Conference in 1913 on the eve of the Great War [3]

But in order to approach this problem in a purposeful fashion we must first assay a definition of normalcy " For every stimulus the correct response " is a dictum first announced by Jeremy Bentham,[4] and one which is as true today as it was 120 years ago Proceeding from this definition we find that it is the incorrect response to a stimulus —many examples, too numerous to cite at this point, might be given—that distinguishes the abnormal individual and marks him an easy prey to environmental stresses Of equal importance is the speed of reaction, both accelerated and inhibited responses being equally pathological [5]

TOUCH AND HEARING

While there are many types of receptors—exteroceptors, enteroceptors, proprioceptors, just to name a few —we will by choice concentrate on two systems which, according to Harry Stack Sullivan, are paramount in determining interpersonal relationships—namely, touch and hearing It is through their help that we can learn to understand those factors conducive to a correct response to stimulation, and the aberrations which the latter may become subject to

It is well known that stimulation of the pacchionian corpuscles sets up a centrally travelling wave of depolarisation [6] The amplitude of each transmitted impulse is a constant one, but, as Adrian has demonstrated so beautifully,[7] the frequency varies with the strength of the stimulus, and it is through modulation of the former, and variations in the area stimulated, that information as to object quality is imparted

Up to now we have only a stimulus and a correct response to it, thus representing a univariable situation similar to that encountered in the nervous system of the cœlenterates, in whom neurotic or psychotic reactions are unheard of [8] However, in 1956 Lowenstein demonstrated the presence of antidromic sympathetic fibres, which had the ability to modify incoming sensory messages [9] Stimulation of these fibres both by electric current and by sympathomimetic agents resulted in an increased response to the applied sensory stimulus When progressively stronger currents were utilised, the sensory fibres finally discharged without being actually stimulated, the result being a clear-cut case of sensory hallucination

Inasmuch as touch occupies a relatively small place amidst the welter of stimuli that by their constant inrush disturb the serenity of the cerebral cortex, we will now turn to the auditory system, where a similar situation has been uncovered Held, as early as 1893, demonstrated the presence of an efferent nerve leading from the area of the superior olive to the cochlea [10] Being educated in the old Viennese tradition,[11] he lost these findings at the Opera-ball in 1894, and it was left for Cajal and Rasmussen to rediscover what is now known as the olivocochlear bundle This tract modulates incoming auditory impulses Galambo's experiments showing that the electrical potential of the cochlear nerve may be inhibited by stimulating these fibres,[12] again demonstrated the degree of cortical control imposed upon receptor organs

These two tracts are only part of what may be termed the gamma efferent system It is this system then, that is implicated in the normal or abnormal response to external stimuli, and which we must further examine in order to find those factors which determine normalcy

DISPROPORTIONATE RESPONSES

Psychiatric literature abounds with cases which will suggest, when examined in this new light, that overactivity or underactivity of the gamma efferent system may precipitate neuroses or severer emotional disturbances

An overactive gamma efferent system is the usual result of sensory deprivation Studies such as those of Lilly,[13] and Meyer [14] show that hallucinations are frequently experienced after removal of external stimuli by either physical or pharmacological means These sensory hallucinations are probably mediated by those very sympathetic fibres described by Lowenstein [9] Mescaline probably acts in a similar fashion, and studies on its effects on the gamma efferent system are now in progress in our laboratories [15]

Conversely, underactivity of the gamma efferent system may make the subject completely immune to external stimulation [16] An interesting, perhaps congenital, example of such an underactive gamma efferent system has been recorded by Mahler [17] Her famous case, Lotta, showed markedly diminished pain sensitivity to the point where one day, out of pure malice, she scorched her lips on a glowing cigar-lighter [18]

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[1] Selye H , et al Proceedings of the 13th Conference on Stress, Monte Carlo 1958

[2] Steinbeck, J Of Mice and Mazes *Arch Calif psych Ass* , 1951, **14**, 211

[3] Adler, A Freud as *I Remember Him* p 121 New York, 1922

[4] Bentham, J Speech in support of the first Reform Bill London, 1832

[5] Lao Tse A hasty man is a public misfortune Translated from the Chinese in Hong Kong

[6] Gray J A B Sato, M Properties of receptor potentials in Pacchionian corpuscles *J Physiol* , 1953 **122** 610

[7] Adrian, E D The Basis of Sensation New York, 1928

[8] Coward, N That Happy Breed p 165 Self Realisation Fellowship, Los Angeles Calif , 1954

[9] Lowenstein, W R Sympathetic receptor facilitation *J Physiol* 1956, **132**, 40

[10] Held, H , Die zentrale Gehorleitung *Arch Anat Entwicklungsgesch* 1893 p 201 (A most interesting reference The only copy extant is on the second floor of the medical library of the University of Wurzburg Ring bell and ask for Max)

[11] Strauss, J Wine Women and Song

[12] Galambo R Suppression of auditory nerve activity by stimulation of efferent fibers to cochlea *J Neurophys* 1956 **19** 424

[13] Lilly, J This is a marvellous paper Someone told me about it at a cocktail party a few weeks ago but I haven t been able to hunt up the reference in time for publication

[14] Meyer J S Greifenstein F Devault M A new drug causing symptoms of sensory deprivation *J nerv ment Dis* 1959 **29** 54

[15] Huxley A Menkes J H Critchley M The neurophysiology of mescaline *Brain (in the press)*

[16] Blow winds and crack your cheeks! Rage! Blow! &c —Shakespeare W *King Lear* iii, 2

Thus it is the disproportionality between the input and the outflow of this gamma efferent system that is responsible for those deviations from normalcy noted in the present generation, and for acts performed which are at variance with the stimulus inciting them (e g, " beatniks ") Why such an important neuronal system should behave in as erratic a manner as it does, is not exactly clear at this time One possibility is that some of the vital relay systems along its paths have become invaded with what we have termed nonconforming neurons, such as previously described for the optic system [19]

Should we accept such a hypothesis, we then acknowledge that the schizophrenic reactions are not directly due to defects on a molecular or enzymatic level, but are the result of disruption on a higher (i e, on a neuronal) organisational plane

Such a theory is very disturbing, especially in the light of the innumerable papers (discretion will not allow me to cite references at this point), which are concerned with determinations of cæruloplasmin, neuraminic acid, tryptophan metabolism, protein centrifugation patterns, &c, &c, all of which are found to be abnormal in schizophrenia, statistically speaking that is

Yet, going back to primary causes, even the organisation of the central nervous system is genetically controlled, and therefore depends on enzymatically directed reactions occurring mainly, or perhaps even exclusively, during the developmental phases A critical reaction might not be able to proceed during this period, resulting in an organisational defect of the gamma efferent system Such a defect, which has as its main abnormality a disproportionate response between input and output, would be in many ways similar to, but infinitely more subtle than, the organisational defects seen in microgyria for instance

FORTHCOMING WORK

In conclusion, we must apologise to the reader, to the editor, and perhaps even to the printer, for having gone so far astray Starting with a neuron, we have jumped in and out of afferent and efferent tracts with results which unencumbered by data, recall Pirandello's *Cosi e, se vi pare* (It is so, if you think so) A fuller discussion of this concept and its application to scientific data and their interpretation will be forthcoming (Pirandello and Scientific Research)

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[17] Mahler, M S Child Psychosis and Schizophrenia *Psychoanal Study Child* 1952 7 286

[18] Ronson Prince Charming S17 85 F O B New York

[19] Menkes J H Progressive non-conformism in the lateral geniculate nucleus of man *Lancet* 1958 ii 1368

THE GEKOCHTEUNDGEBROCHENEEIERSCHALE PHENOMENON

Mechanical and Physiological Factors

BRIAN MAEGRAITH

DENATURATION by heat of the protein content of the encapsulated ovum (or egg) of *Gallus domesticus* has been frequently demonstrated, but a difficulty encountered in all experiments has been the frequent appearance of the Gekochteundgebrocheneeierschale phenomenon

Makewater (1959) has now advanced evidence that in the normal encapsulated ovum a compartment of gas is imprisoned immediately beneath the outer calcareous envelope The well-known law of thermodynamics which states that gas will expand when heated and if confined will exert proportionate stress pressures on the confining medium has been found to apply to the ovum when it is exposed to heat, especially in the region of 100°C The lines of force exerted and their stress patterns in the continuum of the solid envelope are such that inverted implosion may become manifest

Disintegration of the calcareous envelope and consequent escape of the protein matrix during the process of *überkallen*, as Wirtschaftern (1958) designates it, are the two cardinal features of the whole Gekochteundgebrocheneeierschale phenomenon Makewater's contribution to its control is based on the hypothesis that the phenomenon could be inhibited by the creation of artificial escape paths or canals for the enclosed gas, thus obviating hyperdynamic overloading at the pressure surfaces This was accomplished by drilling a critical aperture in the interface between the envelope, the internal ovum, and the liquid environment Trial experiments showed that an artificial communication between the gas-containing compartment in the region of the rounded terminant of the egg-mass acted as a true Gekochteundgebrocheneeierschale inhibitor This of course was achieved by thermodynamic-gas liquid equilibrium which prevented autoclysis

Our own experiments confirm Makewater's observations

EXPERIMENTAL

6 recently delivered enveloped ova were divided into three experimental groups of 2 each On three successive days one group was immersed in cold water and raised to 100 C for two minutes Of the 6 samples, 5 developed extensive envelope stress patterns involving the escape of protein into the liquid environment One sample became " poached (Perkins 1956)

Over a further period of three days three batches each of 2 enveloped ova were heated in the same manner In each case before heating, a Makewater canalisation was performed in the rounded terminant The results were remarkable stress signs were absent and denaturation was absolute

To determine the relative gas/liquid interchange characteristics, a control group of enveloped ova (or eggs) were canalised as above, heated to 100°C for two minutes, and then plunged into cold water containing blue dye (Parker and Stevens 1910) The intradural cavities of each egg accepted some of the pigmented fluid, thus proving Charles s law

Controls, canalised in the pointed (as distinct from the rounded) terminant, were consistently deprived of protein to a degree which led to the condition described by Edelweiss as *hervorgebrochen*

DISCUSSION

With a view to controlling the amount of gas and its distribution within the envelope of the ovum, ortho-oval procedures have been suggested

Addelhauer (1959) has raised donors on a diet of bicarbonate of soda and acetic acid, and claims that by certain postural arrangements he can distribute the gas wherever he so desires within the envelope or shell In this way he has been able to distribute the gas equally at either end of the egg In these circumstances, of course, a Makewater canalisation at either end would serve its purpose during the process of denaturation

Again, certain authorities have proposed that the gas compartment might be redistributed within the envelope by manipulative inversion within the cloaca at the time of, or shortly preceding, delivery Standard obstetric techniques, including the use of forceps, have been proposed for this manipulation

Such problems have not escaped the notice of geneticists For instance, Eierkopf (1958) and Kuru (1957) have pointed out that there are strong indications of the possibility of the appearance of allelomorphic mutants which are determined by mendelian dominant transmission associated with incomplete sex-determined genes which are themselves dependent on relevant chromosomic deficiencies

The importance of this cannot be underestimated Thus, it is clearly possible that allelomorphic mutants may arise which determine the delivery of an egg which is equally rounded (or equally pointed) at both ends If such a mutant were produced it would inevitably be necessary to combine with it an equal distribution of the relevant gas bubble, since if the gas were confined at one end only it would lead to inconsistency in delivery pattern Moreover, if each end were equally rounded and was, moreover, equidistant from the other end, it would be impossible to apply successfully the Makewater technique of canalisation in more than the appropriate mathematical chance ratio (p= <) In such circumstances incubation at adequate temperature, even though it led to denaturation, would not be without risk of the generation of the Gekochteundgebrocheneeierschale phenomenon

On the whole, we recommend that geneticists should refrain from breeding allelomorphic mutants unless they are prepared to develop parallel allelomorphs in donors and operators alike

SUMMARY

If you prick the thick end of a hen's egg, it won't burst when you boil it *Das ist zum brechen*

Public Health

Rehousing the Disabled

In his report for 1959 [1] Dr J A Scott, medical officer of health to London County Council, stresses the difficulty of selecting families for rehousing on medical grounds In 1939 1000 applications backed by medical certificates were received, and, in 1945, 450 But in 1950 they numbered 44,000 An analysis of 1000 certificates in 1947 showed 20% to be genuinely urgent, and 40% less urgent, the remainder contained no grounds for action In 1948 a similar analysis gave percentages of 10, 35, and 55 respectively

Clearly general practitioners were under pressure to produce certificates, and from 1957 onwards the Council asked doctors to send a letter instead, describing any serious medical condition which rehousing might benefit Between 40 and 50 letters a week are now received, practitioners agree that the new system is an improvement

Between 1945 and 1955 the Council rehoused 75,000 families, owing to the growing lack of building sites slum clearance must have priority, but some accommodation is still set aside for medical cases

When a doctor's letter is received, a health visitor is sent to obtain further details, and, whenever necessary, a public-health inspector also reports on the premises The medical officer at divisional level decides whether the application is justified, and the decision to nominate for accommodation is made by the county medical officer of health or his deputy Nominations are then submitted to the housing committee, which considers all the information thus made available

In three years, 521 cases have been recommended for rehousing because of pulmonary tuberculosis, and 1122 for other medical conditions In more than half the cases application is made for accommodation on the ground-floor This is not always possible, often only first-floor accommodation is available Of the first 600 non-tuberculous cases nominated, 174 had locomotor disorders and wished to avoid stairs of these, 30 living on upper floors had had amputations, 41 were arthritic, 40 had lower-limb pareses (poliomyelitic sequelæ), and 31 had disseminated sclerosis Cardiac conditions numbered 164 Often the exertion involved in climbing stairs to a third- or fourth-floor flat within easy reach of the place of work must be weighed against a long and tiring journey to a distant ground-floor flat Priority in cardiac cases is given to those still working and to young mothers bringing up a family Many patients rehoused may not benefit greatly themselves, but the overall improvement in their family's living conditions may be considerable Some refuse offers of rehousing Higher rent is one reason, disappointment at not being offered new premises another Localities must be chosen where the families' personal contacts will not be severed

Dr Scott concludes that it is difficult to lay down any rational set of rules for guidance rehousing is less of a scientific process than an exercise in the practice of the art of medicine

Mental-hospital Admissions by Area

The General Register Office has classified according to the administrative areas in which the patients lived the 88,943 admissions to mental hospitals in England and Wales in 1957 [1] The cases are also classified according to sex, 5-year age-groups, and diagnostic category and into, first or subsequent admissions Admission-rates can be deduced from the Registrar General's population estimates for 1957

While 3 Cardiff residents of every 1000 went into a mental hospital (the highest rate), only 1 2 per 1000 did so in Manchester Wider use of domiciliary, day-hospital, and general-hospital facilities must have contributed to this very low Manchester figure High rates did not characterise industrial areas—in fact, in Cornwall and Norfolk (2 5 and 2 1) the rates were substantially higher than in Staffordshire and Durham (1 7 and 1 6)—but in general the rates were higher in town than in country The highest figures for London boroughs came from Stoke Newington (2 9) and Stepney and Chelsea (both 2 8)

The diagnostic categories are schizophrenia, manic-depressive reaction, senile and presenile psychoses, other psychoses, psychoneuroses, character, behaviour, and intelligence disorders, and other Manic-depressive illness (32 7% of admissions) outnumbered any of the other six categories, with the usual preponderance of women and a peak age of 45 In schizophrenics (20 2% of admissions) the peak age of admissions was ten years earlier, and the sex-distribution was about equal In London the proportion of schizophrenics was higher (28%), but the proportion was greatest in Manchester (36%), rural proportions were lower—e g , in Cornwall (11%) and Hertfordshire (9%)

Unfortunately mental subnormality is grouped with disorders of personality and behaviour, and the figures on which the report is based are but a function of the administrative and diagnostic practices in each area, so that regional differences must be interpreted with caution Thus the report is primarily of administrative interest The incidence of mental illness in the population is a subject in which we lag behind other countries Data showing the changes from year to year would be useful, as would correlation with other variables—for example, bed numbers, average length of stay, day-hospital services, non-statutory beds in general hospitals, and consultant sessions Nevertheless, this report provides valuable pointers to fields in which closer study might be most rewarding

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[1] Report of the County Medical Officer of Health and Principal School Medical Officer for 1959 London County Council Obtainable from the Information Bureau, County Hall S E 1 Pp 166 4*s*

[1] Areas of Residence of Mental Hospital Patients *Stud med Popul Subj* no 16 H M Stationery Office, 1960 Pp 177 15*s* 6*d*

In England Now

A Running Commentary by Peripatetic Correspondents

MOST of the other girls leaving school that year hoped to be nurses or secretaries, but I wanted to be a circus rider There was nothing else for me to do Not in the way of a career So when my headmistress persuaded me that it was *impossible*, I shrugged my shoulders and said, " Oh well I'll have to get married and have six children "

I took my children to the circus for their Christmas treat It was their choice but I was pleased They all laughed when a dwarf squirted water from the top of his head The boys liked the tigers and the clowns But when a big white horse sauntered round the ring and a girl in sequins turned somersaults on his back, I glanced at my daughter, Emmeline There was a look in her eyes that I had never seen before

The dwarf who squirted water from his head jumped up and down in front of us and said, mysteriously, " Your turn will come " While two shining acrobats writhed in a crescent moon high above our heads I saw, in the darkness below, five men, a tall pole, a long rope, and a pulley When the lights went up the ringmaster said, " Now we want a member of the audience to do some bareback riding " At my side, Emmeline gasped, half rose to her feet " Anyone over the age of eighteen " " Oh," moaned Emmeline " I'm only six Even the boys aren't eighteen " " Will any gentleman in the audience come forward ? And it doesn't have to be a gentleman Perhaps a lady would like to try ? Come along Come along " " Go on, Mummy," whispered my eldest " It's the chance of a lifetime "

I stood in the ring Too late I remembered my straight, tight skirt, but I comforted myself with the knowledge that my legs were still presentable They tied a broad leather belt around my middle and hooked me to a rope Across the pulley a man held the other end The big white horse cantered in The gates closed " Now," said the ringmaster " Run and jump We won't let you fall "

I ran and jumped and missed Not a hope Screams of laughter Wolf whistles " Try again " I tried This time as I jumped I floated through the air and managed to grab the two handles on the horse's back I was up astride My skirt slid upwards Nylons, suspenders, more wolf whistles But I didn't care Round and round we went I knew this was the life for me " Now on your knees!" Easy I held on tight and twisted I was kneeling, quite secure on that broad white back I could even see the faces in the half-light as we circled I grinned at my children Emmeline's mouth hung open " Now on your feet!" This wasn't so good But the friendly tug of the rope as it tightened across the pulley gave me confidence In a moment I would be there, standing up, perhaps even dancing Just a question of balance Now Up Do it slowly Take care Up Now, let go

I swayed and moved my leg outwards to keep my balance But I forgot my skirt The rope jerked as I grabbed at the handles The world turned over and I swung through the air Far away I could see the horse still cantering round the ring I swung back across his head, and below I could see the faces of my children, the boys laughing, Emmeline worried Then I swung away again, dangling helplessly in the air The mother of six who wanted to be a circus rider

The boys are still very proud of their mother, which is comforting But Emmeline hopes to be a nurse when she grows up

* * *

Yesterday I came across a little-known side-effect of systemic penicillin therapy A patient with an infection of the upper respiratory tract was advised to have penicillin by injection He agreed, but asked, " Can I have it in my right arm, doctor ?" " Certainly, are you left-handed ? ' " No But when I have it in my left arm my watch stops '

* * *

Let's make it a National Health Service Christmas—join our Christmas Club and shop at the surgery! Ask your Doctor NOW for your FREE copy of the Ministry of Health's fabulous 800-page illustrated catalogue of Special Shilling Gift Parcels! YOU choose them, WE send them! May we suggest

The Home Surgeon Kit —Create your own emergencies for Ward 10! Contents include set of tools and complete instructions—e g , " Your gallbladder and how to remove it

The Hypochondriac's Hamper —Contents include 250 tranquillising capsules (with the exciting new centres) and choice of twelve disconcerting Aperients Also Stomach-pump, A C or D C (with little robins on the lid, postage and packing extra) One copy of H M S O publication *How to tell How You Are*

The Gay Deceiver Gift Parcel —Contents include Wig (choice of six smashing styles, including the chrysanthemum, etc), one pair rose-coloured spectacles, one set dentures, deaf-aid, and choice of artificial limb and/or kidney, glass-eye, elastic hosiery or corsets One copy of H M S O publication *What Are Little Girls Made Of*

The Soho Special —Packed in handy cosh-sized Christmas stocking Contents include razor with spare blades, brass knucks, nine inches of bicycle-chain, and a packet of assorted wound-dressings Also vouchers for FREE ambulance get-you-home service, six novel suggestions for alibis, and a psychiatrist s certificate guaranteeing the bearer is not responsible for anything

Customers will thrill, too, at the Ministry's sticky Yule-tide labels, bearing seasonable greetings, such as " One tablespoonful three times a day in water " and " Stow away from Boilers "

General Practitioners of course can hardly wait for details of the Ministry's competition for Ye Beste Decorated Quainte Olde Englysshe (Brittisshe) Waiting-Roome, with contemporary periodicals

There will be inspections of all Festive Premises to detect any reactionary deviationists and to ensure that over Christmas such premises are kept open day and night, with the General Practitioner greeting the customers by emerging from the waiting-room fire-place disguised as Father Christmas

* * *

During last week's rainy weather it was reported that the angels in Regent Street had all mysteriously developed abdominal distension and swung in apparent celestial pregnancy above the milling shoppers Mr Beverley Pick, their designer, was greatly disturbed by their changed appearance, and treatment was instituted by attaching a sharp spike to the end of a long pole which was then thrust into each angelic abdomen But does not this treatment by remote-control paracentesis suggest that the true diagnosis should really be Pick's disease ?

* * *

I am a great believer in toothpicks Since I began using them three or four years ago I have had no caries whatever I suppose dentists do not advocate them more freely because of the risk of their being used *ill*-manneredly Perhaps the toothpick is in a position opposite to that of war, which Oscar Wilde said would have its fascination as long as it was regarded as wicked when it was looked upon as vulgar, it would cease to be popular Let us, then, have a campaign to emphasise the toothpick's exciting association with wickedness let each Sir Jasper in every melodrama be a flagrant user of these dastardly instruments

* * *

My first Christmas card of this season came from a friend in New York My appreciation of this Yuletide greetings was only a little marred by the bold postmark on the envelope—Report Obscene Mail to your Postmaster

* * *

CAROLS FOR PSYCHIATRISTS

I

Hurrah for crime and sex anomalies,
Perversions all and problem families,
Without which at this festival
We would not have the wherewithal

II

To comfort always is our task I hear,
But tranquillisers now give way to beer
And from neurotics sad or frisky
Thankfully I turn to whisky

Letters to the Editor

THE CASE AGAINST TRENDELENBURG'S POSITION

SIR,—I have been waiting for others to scramble into the arena and pick up the glove trailingly thrown, not only by your annotation, but also by Dr Inglis in your issue of Dec 10, and previously by Dr Inglis and Mr B N Brooke[1]

From Celsus (40 B C) and Abulcasis of the 11th century, down to Percivall Pott of the 18th, and modern times, the semi-inverted position has been used for the treatment of abdominal injuries and replacement of intestine, for the simple reason that the ancients instinctively recognised that this position induced a negative pressure in the abdomen It was, however, Friedrich Trendelenburg (1884–1924) who first observed that " when the peritoneal cavity is opened with a patient at an angle of 30–40 degrees, a negative pressure sucks air into the cavity with an audible sound, and as a result the intestines bunch together in the epigastrium, so causing no concern to the surgeon ", and he goes on to state that " every step of a pelvic operation can then be done under direct vision ", a thing which is absolutely true

In a long career and experience of many countries, I have yet to see the postoperative shock or cardiovascular and pulmonary disasters experienced in Birmingham from the use of the Trendelenburg position in these days of skilled anæsthesia and relaxants Certain it is that a moderate inverted position is essential for a Wertheim or any high-class difficult surgery of the tubes Moreover, as was shown by Spalding in his classic paper[2] which was backed by Sir Heneage Ogilvie, when such patients are put back to bed in a prone position rather than Fowler's, drainage, and particularly lymphatic drainage, is better and recovery more speedy, with less risk or incidence of thrombosis and embolism

If there be any banishing, by all means let the gynæcologist give up the cosmetic bikini-wishing Pfannenstiel (1862–1909) incision This indeed is a real relic of the bad old days of anæsthesia, possessing multiple disadvantages, the greatest being that removal of the large tumour and/or complicated pelvic surgery is made a nightmare of inefficiency Indeed, unless both recti are really cut across it is impossible to see or do properly any delicate or complicated work with that celerity and bloodlessness that modern technique demands

London, W 1 V B GREEN-ARMYTAGE

SIR,—Apart from the six objections—respiratory and cardiovascular complications, calf-vein thrombosis, nerve injuries, late shock, and an irritated anæsthetist—mentioned by Swain,[3] there is another possibility referred to by Abel and Lewis[4] They described local baldness in eight women who had had long gynæcological operations, mostly with Trendelenburg tilt The baldness was fortunately reversible The histological changes seen in the skin could be reproduced experimentally in cats by circumscribed pressure on the head

Amsterdam T WILHELMUS

CHEMOPROPHYLAXIS IN CHRONIC BRONCHITIS

SIR,—I would be grateful for a chance to comment on your leading article of Dec 10

Of course the chronic bronchitics described in the Swiss trial improved they had been removed from their usual environment and were getting rested in hospital The drugs they received were of minor import

But what of the chronic bronchitic in his normal (" normal " in the sense of " usual ") habitat?

There he sits, poor fellow, in his damp house, with factory and power-station chimneys all around He's been at work all day, queuing in the rain afterwards for an overcrowded bus On the mantelpiece, within easy reach, is a jar full of ' Omnimycin ', and he has been told to keep on eating them for the next few months

It's all like Grandma's Daily Purge to keep her Bowels Moving

London, S W 11 R WINSTON

HOSPITAL SHOPS

SIR,—I am impressed by the argument in your correspondence columns of Dec 3 and 10 concerning the illogicality of the sale of cigarettes in hospital shops

I have discussed the matter with a number of my colleagues who are all, I find, in general agreement with the principle involved

There are, however, a number of modifications in the views expressed dependent on the special interests of the doctors concerned The ophthalmologist feels that cheap books with small print are undesirable the psychiatrist is doubtful about the large print in the newspapers the rheumatologist, pædiatrician and diabetic physician agree in condemning the sale of sweets and chocolates The casualty surgeon, noting the increased incidence in domestic burns, would prefer that matches be not sold It was a misanthrope who suggested " Get well " cards were also illogical

PRO BONO PUBLICO?

RADIOLOGICAL HAZARDS TO PATIENTS

SIR,—I should like to go further than Dr Gibson (Dec 3), who re-emphasises the dangers and inadequacies of fluoroscopy in the detection of early pulmonary tuberculosis, and suggest a complete reappraisal of the value and limitations of fluoroscopy generally in diseases of the chest

Apart from its rare use in detecting abnormal movement of the diaphragm and irregular cardiac behaviour, it is doubtful whether fluoroscopy should ever be used as a *preliminary* measure

The safer procedure is to obtain a postero-anterior radiograph first, supplemented by further projections and possibly fluoroscopy as indicated by the initial radiograph Intrinsic disease of the œsophagus, of course, is an indication for fluoroscopy

It should be realised that the use of image intensifiers, whilst giving a greater illumination of the field and reducing the dose to the patient as compared with conventional fluoroscopy, still leaves unsatisfied the requirements of a permanent record and a rough idea of the radiation dose received by the patient

Sheffield THOMAS LODGE

SIR,—Your leader of Dec 10 implied that the manufacture of diagnostic machines as alternatives to radiological equipment (i e , foreign-body locators) is now contemplated in this country

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1 Inglis J M Brooke B N *Brit med J* 1956, ii, 343
2 Spalding J E *Lancet*, 1946, i, 643
3 Swain J *Med J Aust* 1960 ii 536
4 Abel R R Lewis, G W *Arch Derm Syph* 1960, 81, 34

Your readers will doubtless be interested to learn that this matter has engaged our attention and research for the past two and a half years, and that a foreign-body locator is now in production While one of the initial production batch was in use at a leading Midlands hospital, recommendation was made for us to attend the physics department of a London hospital particularly interested in this subject, with a view to adapting our machine for work other than the purely ophthalmological uses for which it has been primarily designed

Accordingly the machine equipped with only the standard ophthalmological probes was tested for location of a needle fragment in a patient's back The test was immediately and outstandingly successful, as a result of which further specifically designed probes are being prototyped for location work on parts of the human body other than the eyes

This company will be happy to reply to all inquiries concerning the detailed specification of this foreign-body locator

F N HAM
General Manager,
Keeler Optical Products, Ltd

London, W 1

COST OF THE HOSPITAL SERVICE

SIR,—A daily newspaper has drawn the attention of its readers to the alarming rise in the cost of the Hospital Service I suggest that the fault lies partly in the Government's attitude to general practioners in this country

The cost of the Hospital Service together with the long period of waiting for outpatient appointments could be reduced in two ways

Firstly, pathological and X-ray facilities should be available to all practitioners

Secondly, some form of grant and inducement payment should be made to general practitioners who wish to do their own minor surgery This would allow the consultants more time to devote to the more important cases while allowing the young practitioner to exercise the skill he acquired when doing his numerous house-jobs, which is at the present moment entirely wasted

Newport
Isle of Wight

J A C TERRY

POSTPARTUM PRE-ECLAMPSIA

SIR,—Dr Salzmann (Dec 3) is largely though not essentially in agreement with my hypothesis

He agrees that (*a*) corticosteroid increase is not of primary significance in pre-eclampsia, (*b*) the contracting uterus post partum and intrapartum provokes renal ischæmia, and (*c*) ergometrine heightens uterine activity

He differs from me in believing that the products of decomposition of the red infarct provoke renal ischæmia, whereas I have shown that the resistance to stretch of the myometrium is responsible for this renal change in pregnancy and post partum, both experimentally and from clinical data Franklin and I have further shown that renal ischæmia can be produced by nephrotoxins even to the extent of a complete renal shutdown, and Dr Salzmann s view based on Professor Young's observation cannot be entirely denied

But we do know that red infarcts are present without pre-eclampsia accompanying them, while the toxæmic state can exist in their entire absence, and there is no correlation between their extent and the degree of toxæmia Neither can they be used to explain the difference in incidence of pre-eclampsia in primiparæ and multiparæ

Dr Salzmann raises the point that even in the premature and very small baby toxæmia can supervene and thereby appear to upset the uterorenal thesis This apparent contradiction can be explained by the following facts The kidney of chronic hypertension (in which evidence is accruing of renal ischæmic changes [1]) would reasonably be expected to be more responsive to the uterorenal reflex, the vascular effect on myometrium showing chronic hypertensive changes would be earlier and more marked and fœtal growth thereby impeded This is supported by the brilliant research of Mr G W Theobald, who, in interrupting the uterorenal reflex pathway by denervation of its tract, succeeded both in increasing the fœtal size (and securing viability) and in preventing toxæmia, hitherto an accompaniment of these pregnancies

Worthing

J SOPHIAN

BLOOD-CHOLESTEROL AND ASPIRIN

SIR,—In a preliminary communication (Nov 19) Dr Eidlitz reported that aspirin (1 5 g daily) reduced the blood-cholesterol level in 10 patients with cardiovascular disease In a group of 21 hypercholesterolæmic patients, to whom aspirin was administered for eight weeks, we [2] found that doses of less than 4 g daily usually failed to lower serum-cholesterol More than 5 g of aspirin daily produced a significant and consistent fall in serum-cholesterol but no change in the cholesterol-phospholipid ratio or the beta-lipoprotein cholesterol These observations also indicated that during aspirin therapy the serum-cholesterol levels are inversely related to the level of serum salicylate With a dose of 5 g aspirin daily, the incidence of side-effects was so high that we did not think that aspirin was a practicable treatment for the reduction of hypercholesterolæmia A satisfactory explanation of these contrasting findings is not immediately obvious

W D ALEXANDER
Glasgow A I MACDOUGALL
M F OLIVER
Edinburgh. G S BOYD

MENTAL OBSERVATION WARDS

SIR,—Although I am more concerned myself with the psychological conclusions to be drawn from mental observation-ward practice, I think Dr Gooddy and his colleagues (Dec 10) may be interested in a clinical table of patients seen in the unit at St Francis Hospital, East Dulwich, during part of the years 1949–50 [3]

Stone House,
near Dartford
Kent

J P CRAWFORD

"THEY NEVER TELL YOU ANYTHING "

SIR,—I agree with Dr Loudon (Dec 3) that the "of course they never tell you anything" of those patients that leave hospital is seldom true in its literal sense—but not always Everybody knows that many patients leave hospital with little knowledge of what is wrong with them, because somebody has forgotten or failed to explain to them their diseases in plain language

Everybody talks as well of how overcrowded the outpatient department is, but this is no excuse for the many who say they cannot waste time explaining "everything" to the patient

All every patient wants to know is the answer to the questions (1) what is wrong with me? (2) how bad is it? (3) how long will it last? (4) what treatment are you going to give me? (5) shall I be "all right" afterwards? By making a rule to answer all these 5 questions for every patient before he asks them, very little time is spent and very many worries and troubles are spared to the anxious patient

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[1] Cook W F Renal Association meeting Oct 27 1960

[2] Alexander W D Macdougall A I Oliver M F Boyd G S *Clin Sci* 1959 18 195

[3] *Practitioner* 1954 173 696

This applies particularly to the surgical patient. It must be realised that an operation, however trivial, is the utmost event in the lives of most patients, so no wonder they are so concerned, wanting to know the smallest details that may seem ridiculous to us but are an enigma to them.

Winford Orthopædic Hospital,
near Bristol
J. S. BAENA

TREATMENT OF OBESITY BY THE HIGH-FAT DIET

SIR,—I read with considerable interest Professor Yudkin's and Miss Carey's article (Oct. 29) as well as Professor Yudkin's letter of Dec. 10.

I have for the past two years been following a diet such as they describe. It is effective in controlling a tendency to overweight, and the difficulties pointed out by Dr. Sasieni (Nov. 12) are not insurmountable. Other problems arise, however, in the long run: a certain amount of hunger is inevitable (and yet more protein is no answer since this increases the calorie intake and thus weight) and over many months this nagging hunger leads to irritability and nervousness. Moreover, even after eating habits have been changed, total adjustment to this diet is hard to achieve; it does demand an unceasing self-discipline, and this too imposes a cumulative burden of strain.

I wonder whether many of Professor Yudkin's patients have happily followed this diet over a number of years without suffering any such stress in the long run?

Queen's University,
Belfast.
LILIAN R. FURST

ASSESSMENT OF CEREBRAL BLOOD-FLOW WITH RADIOACTIVE TRACER

SIR,—We have been studying[1][2] the cerebral circulation by a method similar to the now widely used technique of following an injected tracer during its transit through the heart with an external scintillation counter.

To study the cerebral blood-flow (C.B.F.), 30–50 µC of ^{131}I-serum-albumin are given by rapid intracarotid injection, and the passage of the tracer through the cerebral vessels is recorded by a directional scintillator. The counter is placed on the head, on the same side as the injection, and is connected to a ratemeter and a writing recorder.

The tracings (radioencephalograms, R.E.G.) show a sharp rise, followed by a short plateau, and a dropping phase (see figure). By plotting the tracings on semilogarithmic paper, the last part of the curve becomes linear, following an exponential law, and can be expressed by its half-time ($T_{0.5}$): $\frac{0.693}{T_{0.5}} = R$, the fractional turnover-rate of the cerebral blood-volume. In normal cases $R = 0.24 \pm 0.037$.

$R = \frac{\text{C.B.F.}}{\text{cerebral blood pool}}$ and increases after the inhalation of 5% CO_2 in O_2, in accord with the increase in C.B.F., demonstrated by the nitrous-oxide technique.

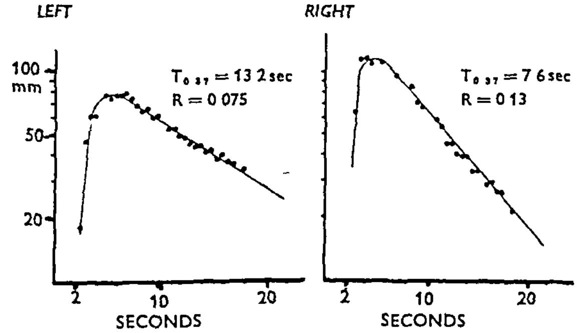

Fig. 2—Plotting on semilogarithmic paper: left, thrombosis; right, normal.

Significant differences in the R.E.G.s on one side and the other are observed in patients with thrombosis of one interal carotid (see figure).

We have found this method easy and innocuous, and we think it well suited for revealing gross alterations in cerebral blood-flow.

University of Genoa.
C. FIESCHI
F. DI PIETRANTONJ

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1. Fieschi, C., Di Pietrantonj, F. *XIII Congr. Naz. Neurol.* Messina, May, 1959.
2. Di Pietrantonj, F., Fieschi, C. *Minerva Nucleare*, 1960, 4, 81.

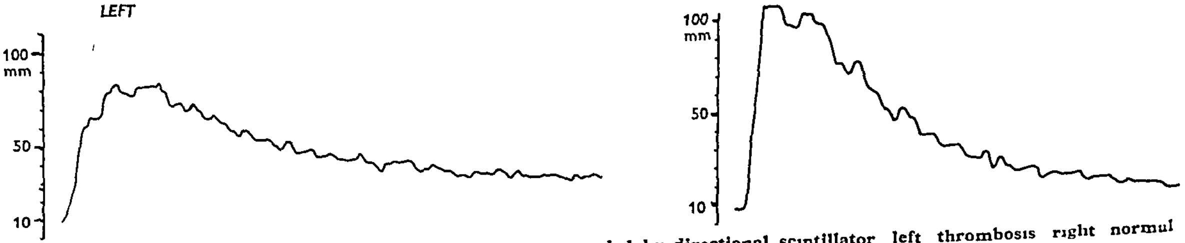

Fig. 1—Passage of tracer through cerebral vessels as recorded by directional scintillator: left, thrombosis; right, normal.

PROTEIN IN HYALINE MEMBRANE

SIR,—In your excellent summary (Nov. 5) of new concepts in hyaline-membrane disease the statement that "no effective remedy is in sight" is perhaps unduly pessimistic.

The syndrome is characterised by progressive sternal and intercostal retraction, and that this is a clinical manifestation of abnormally high intrathoracic negative-pressure swings is now common knowledge. Exerted some forty to fifty times a minute, these alone are theoretically capable of damaging the pulmonary capillaries of a premature infant.[1] Moreover, a high negative pressure increases the pressure gradient between pulmonary capillaries and alveoli,[2] and this may well constitute the driving force of the exudate from which the hyaline membrane is ultimately derived.[3] If this reasoning is correct, then positive-pressure lung inflation, by diminishing capillary trauma and by reversing the pressure gradient between capillaries and alveoli, should be the logical treatment.

Attempts to put these views into practice in the past two years have admittedly been disappointing. The infants so treated, however, were small bad-risk premature babies weighing only 1¹/₂–3 lb., and were in the terminal stages of the disease. Continuing sternal retraction suggested that high enough pressures were not being used, and, in the absence of a mechanical ventilator, efforts were probably not persistent enough. It is perhaps insufficiently realised that our knowledge of the pressures used in lung inflation stems largely from work done on

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1. Barrie, H., Bonham Carter, R. E. *Brit. med. J.* 1959, i, 1183.
2. Burton, A. C., Patel, D. J. *J. appl. Physiol.* 1958, 12, 239.
3. Barrie, H. *Brit. med. J.* 1960, i, 420.

excised lungs with airtight cannulæ In practice, higher pressures are necessary and this work requires urgent reinvestigation with the free-lying endotracheal tubes at present in common use Also, for positive-pressure respiration to be effective in hyaline-membrane disease, it would need to be used, from theoretical considerations, from the onset of the disease Our faith in the value of positive-pressure respiration has been strengthened by our recent experience with a 2½-lb premature infant with severe hyaline-membrane disease who was successfully ventilated for 60 hours, when death occurred as a result of cerebral hæmorrhage There have also been two reports of this method of treatment with survival First, Benson's group,[4] using tracheostomies and curare, and now Colgan and coworkers,[5] using endotracheal intubation, have successfully treated four infants with respiratory distress by prolonged mechanical positive-pressure ventilation Whilst none of the four infants had a birth-weight of under 5 lb, the results are sufficiently encouraging to merit a trial of this treatment for hyaline-membrane disease

St Thomas's Hospital
London, S E 1

HERBERT BARRIE
R P WISE

CANCER OF THE ŒSOPHAGUS

SIR,—We should like to thank Mr Dark (Dec 3) for his interesting and constructive suggestions, but we do not share his enthusiasm for the Mousseau-Barbin œsophageal tube We do not feel it fulfils all our requirements The largest Mousseau-Barbin tube has an external diameter of 16 mm and the lumen is barely large enough to allow the patients to swallow semi-solids The largest tube we use has an external diameter of 1 inch (25 mm) and enables the patient to eat a normal diet provided that fluids are taken frequently during the meal

The main point of our argument is that a malignant stricture of the œsophagus can be dilated very much further than one might think would be possible without the wall splitting, this fact is not widely appreciated The chief disadvantages of the Mousseau-Barbin tube are that its lumen is too small and it is expensive

Finally, we should like to stress once again our belief that it is safer to dilate the stricture by pulling something through from below than attempt dilatation through an œsophagoscope

Royal Marsden Hospital
London S W 3

W P GREENING
GORDON S RAMSAY

PNEUMOCONIOSIS

SIR,—Working among a mining community, I am concerned how often some men are told, by consultant physicians, chest physicians, and their own doctors, that they have pneumoconiosis, when there is little radiological evidence for this diagnosis Very often this opinion is expressed without a true knowledge of the radiological appearances of category-2 (certifiable) pneumoconiosis

When such an opinion is given it is not often realised that the aftermath can be that the patients are rejected by the pneumoconiosis panel At best, the patient feels doctors do not know their own minds At worst, it leads to the development of symptoms where none existed, to unnecessary changing of jobs and economic difficulties, and to a permanent grudge in a man who feels he is being denied compensation

Most miners who have worked a lifetime in the pits come to expect a certain amount of ' dust on their lungs " If radiological evidence confirms this, then the man should be told in these terms, qualified by advice to apply to the pneumoconiosis panel who will be the final arbiters and decide whether the amount of dust justifies certification The man will then feel that he has had good advice but, at the same time perhaps, be relieved to learn that the dust on his lungs is not sufficient to be classified as pneumoconiosis

Worksop Notts

A F OAKLEY

SIMULTANEOUS THROMBOTIC THROMBOCYTOPENIC PURPURA AND AGAMMAGLOBULINÆMIA

SIR,—Many authors have classified thrombotic thrombocytopenic purpura (T T P) as a so-called collagen disease and accepted an immunological pathogenesis based on an antigen-antibody reaction The recent observation of T T P in two children with agammaglobulinæmia and an adult [1] with a partial antibody-deficiency syndrome is against this hypothesis

CASE 1 —A boy of 16 months with congenital agammaglobulinæmia and constant lymphopenia developed an acute febrile illness within 24 hours of a combined vaccination with triple antigen and T A B The hæmoglobin fell from 16 to 4 8 g per 100 ml in 3 days (reticulocytes 19 2%, platelets 84 000, bilirubin 1 4 mg per 100 ml , direct Coombs test negative) No abnormal antibodies could be detected in the indirect Coombs test in saline and in albumin at various temperatures The child died 14 days after the vaccination Necropsy revealed typical subendothelial and intravascular fibrinoid deposits in the capillaries and arterioles of virtually all organs

CASE 2 —A girl of 6 months entered hospital because of anæmia and vomiting Hæmoglobin 5 6 g per 100 ml (reticulocytes 7 2%, platelets 79,000, bilirubin 3 mg per 100 ml , direct Coombs test negative) No abnormal agglutinins were detected with the indirect Coombs test in saline and albumin at various temperatures Paper electrophoresis revealed no gamma-globulin The cause of this agammaglobulinæmia is unknown It is unlikely that it was of a congenital hereditary origin A right-sided hemiplegia developed and she expired, despite corticotrophin therapy, a month after admission Necropsy showed the same changes as in case 1

CASE 3 —A 52-year-old mason had two episodes of aphasia and mental disorientation followed by rapid deterioration, progressive pyramidal signs, purpura, jaundice, and death within 2 months of the onset of symptoms Hæmoglobin 8 g per 100 ml (reticulocytes 23 5%, platelets 33 000, bilirubin 5 2 mg per 100 ml) Direct Coombs test negative No abnormal agglutinins were detected in the indirect Coombs test at various temperatures in saline or albumin medium L E test negative Immunoelectrophoresis no β_{2M}-globulins The absence of this line is a constant finding in the antibody-deficiency syndrome Necropsy confirmed the clinical diagnosis of T T P

In addition to the association of T T P with agammaglobulinæmia, the negative Coombs test in our patients and in the great majority of the published cases is further evidence that the hæmolytic anæmia is not the result of autoimmunisation Furthermore it has never been possible to demonstrate platelet antibodies in T T P

The pathogenesis of this curious syndrome remains an enigma Theoretically, the underlying mechanism may be similar to that in the experimental generalised Sanarelli-Schwartzman reaction, in which the vascular lesions are identical to the ones observed in T T P Thrombocytopenia is a feature of the experimental syndrome, but hæmolytic anæmia has not been observed The development of T T P within 24 hours of vaccination in case 1 could be compared to the effect of the provoking injection of endotoxin in the experimental animal with the generalised Sanarelli-Schwartzman reaction

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[4] Benson F Celander O Haglund G Nilsson L Paulsen L Renck L *Acta anæsth scand* 1958 2 37

[5] Colgan F J Eldrup-Jorgensen S Lawrence R M *J Amer med Ass* 1960 173 1557

[1] Frick P G Hitzig W H *Schweiz med Wschr* 1959 89 55

Department of Medicine and Pediatrics,
Kantonsspital,
University of Zürich

P G **Frick**
W H **Hitzig**

SIMPLE ULCERATION AND CANCER

Sir,—In your annotation of Dec 10 you stress the growing acceptance of the view that there is a correlation between the two You point out the frequency with which carcinoma follows ulceration of skin and colonic epithelium, but you regard the rarity of malignant change in duodenal ulceration as an anomaly

The paradox can be explained readily on the assumption that cancer develops not merely because of the stimulus of chronic ulceration but as a result of the interaction of the stimulus and the genetic instability of the epithelium The same stimulus may produce quite different effects on the epithelium of skin, duodenum, ileum, and colon Neoplastic mutation is rare in the mucosa of the small bowel, and prolonged ulceration does not succeed in increasing materially its frequency In the colon, however, carcinomatous mutation is common and the effect of longstanding ulceration is to increase the risk of malignant change about thirtyfold The mechanism of this is unknown it may be a direct chemical phenomenon or merely the result of increased rate of mitosis (and therefore increased chance of mutation) in the healing phase It is significant that carcinoma develops most frequently in those patients whose colitis is in remission

Regional ileitis has been observed for a sufficient length of time for it to be apparent that it is only rarely complicated by carcinomatous change Only recently, however, has it been recognised that Crohn's disease not infrequently affects the colon Cases of this type have been followed for only a few years It would be anticipated that carcinoma will develop with a frequency similar to that in ulcerative colitis The potentiality of the affected epithelium is more important than the disease producing the ulceration

In view of the rarity of spontaneous carcinoma of the duodenum, jejunum, and ileum it is not surprising that chronic ulceration fails to induce neoplastic changes in them The only anomaly is the rarity with which benign gastric ulcer is followed by carcinoma

St Mark s Hospital,
London, E C 1

A G **Parks**

Sir,—Your annotation of Dec 10 gives interesting clinical data on the part played by ulceration in the genesis of cancer

I have carried out animal experiments at this hospital and my preliminary findings confirm your observations It appears that three factors are involved in carcinogenesis

(*a*) The exposure of the epithelial basal cells, such as would occur in certain anatomical sites, in acute ulceration, and in the early stages of wound repair

(*b*) The direct access of an exogenous carcinogen to such a denuded area

(*c*) The duration of contact between the cell and the carcinogen [1]

In a series of experiments on rats' stomach carcinogens were administered by stomach tube or by local application via gastrostomy A number of animals of the latter group were also subjected to chemical or surgical ablation of the gastric mucosa In the experimental group this pretreatment was followed by topical administration of carcinogens, whereas the controls received gastric injuries only There were no local tumours among 66 rats fed by stomach tube but several mammary tumours were elicited Nor were there tumours among 14 rats whose stomachs were injured or ulcerated Among 101 rats given carcinogens via gastrostomy with or without concomitant ablation of the mucosa, 10 animals developed gastric tumours including squamous, adeno, and anaplastic carcinomas 2 tumours weighed as much as 80 g, and 4 yielded widespread metastases

Your question regarding the paucity of cancers in duodenal ulceration may be answered by reference to the three criteria which, if combined, lead to the development of cancer The passage of foodstuff varies in the different segments of the digestive tract, being rather slow in the stomach, colon, and rectum and fairly rapid in the first part of the duodenum The possible mechanical or chemical irritants of the digested food would thus quite naturally affect ulcers in stomach, colon, or rectum more readily than those in the duodenum Even quiescent lesions may, in their acute stage, have been affected by such irritants and the cancer arising therein may only become apparent after a long latent period

I have carried out a number of other, similar, experiments on skin, cervix uteri, and tongue of laboratory animals and preliminary findings suggest the general applicability of the " three-criteria theory "

Marie Curie Hospital,
London, N W 3

R **Stein-Werblowsky**

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[1] Berenblum I, Haran Ghera, N, Trainin, N *Brit J Canc* 1958, **12** 402

KIDNEY HOMOTRANSPLANTS

Sir,—Dr Benirschke's plea (Oct 29) for more extensive records of placentation was pertinent in the study of the relation of the type of placental circulation to the histocompatability status in twins I wish to add a few isolated experimental findings to his comments

In the course of recent experiments at the Postgraduate Medical School, London, the following incidental observations were made Conventional rejection of skin homografts occurred in 10 cases (8 rats from one litter and 2 dogs from a single litter) The circumstances of placentation in these animals is, of course, unknown However, it is extremely unlikely, at least in the rats, that there was vascular communication between adjacent placentas The discrete placement of the sites of placental attachment along the uterine horns in rodents is well known and its mechanism has occasioned much research

Apposed placentas are found [1] and can be induced in the mouse, Ladman [3] demonstrated histologically the consistent presence of a septum of maternal connective tissue between the two placentas The only real union of fœtal tissues found was that of contiguous Reichert's membranes, anastomoses between placental labyrinths or fœtal blood-streams was unlikely In the rat, Huber [4] reported the presence of two egg cylinders in one decidual crypt, he regarded the occurrence as extremely rare Carr [5] considered the discovery of a single case of placental fusion important enough to report No mention of circulatory confluence between placentæ was made by Boe [6-8] who made extensive and meticulous studies with indian-ink injection and corrosion preparations in the rat

This evidence, though tenuous, supports Dr Benirschke's contention to some degree, and emphasises the need for a precision in classifying multiple embryos such as recommended by Boyd et al [9] and originally suggested by Hamlett et al [10]

Boston, Mass

John Anderson

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1 Carr, J G *Proc roy Soc Edinb B*, 1945 **62** (part 2, no 22) 189
2 Smithberg M *Anat Rec* 1955 **121**, 368
3 Ladman A J *ibid* **125** 41
4 Huber G C *J Morph* 1915, **26**, 359
5 Carr, J G *Proc roy Soc Edinb B*, 1947, **62** (part 3, no 36) 304
6 Boe F *Acta endocr Copenhagen*, 1950 **5**, 356
7 Boe, F *ibid* p 369
8 Boe, F *ibid* 1951, **7**, 42
9 Boyd J D, Hamilton, W J *in* Marshall s Physiology of Reproduction (edited by A S Parkes), p 42
10 Hamlett, G W D, Wislocki, G B *Anat Rec* 1934, **61**, 81

HOSPITAL INFECTION

SIR,—Your comments (Dec 3) on a new and valuable book on hospital infection, include the statement that the 'mode of transmission" of staphylococcal infection in hospital wards "is still obscure" This seems to me to be obscurantism or perhaps agnosticism in excelsis

The staphylococci are carried into the ward in or on the bodies of patients and their attendants, and are distributed in the ward by the clouds of dust from bedmaking and brisk movements of persons in the wards The stores of staphylococci are to be found in blankets (woollen), in the interior of mattresses and pillows, in floor dust, and in the noses of persons in the wards In maternity wards infants' noses and umbilicuses are reservoirs of pathogenic staphylococci

Blankets should be laundered at short intervals (every ten days in a maternity ward) and be sterilised while being washed Mattresses and pillows should be treated in the hospital formalin disinfector, preferably every ten days All attendants should wear effective sterile masks and gowns The floors should be cleaned with effective vacuum cleaners, not brushed with brooms To avoid transmission by their hands nurses should wear thin sterile rubber gloves None of these precautions is difficult, nor should nursing routine be disturbed

St. Margaret s Hospital,
Epping

FRANK MARSH

BENZHEXOL IN MULTIPLE SCLEROSIS

SIR,—The course of multiple (disseminated) sclerosis is seldom influenced by treatment, and the following case is recorded because useful, if slight, diminution in disability was achieved with drugs

A married woman had retrobulbar neuritis at the age of 23 in 1943 In 1949 she had a normal pregnancy In 1950 investigation for fatigue and weight-loss revealed no definite abnormality, but two years later multiple sclerosis was diagnosed on the basis of temporal-disc pallor, asymmetrical limb reflexes, extensor plantar responses, slight nystagmus, and a paretic Lange cerebrospinal-fluid curve

When she came under my care in 1953, she tended to fall to the left on walking and had diplopia on looking to the left In 1956 a left retrobulbar neuritis developed, followed by a right-sided attack, at this time frequency and hesitancy of micturition and awkwardness of the right foot also began In 1957 paræsthesiæ developed in both lower limbs and her gait got worse, but with a stick she still walked half a mile to work each day In September, 1959, she finally became housebound, needing the support of walls or furniture every two or three steps During the previous eight years she had had, at various times, without benefit, injections of vitamin B_{12}, isoniazid, and nicotinic acid and prednisone

In May, 1960, there was disc pallor, exaggerated tendon reflexes, ankle clonus, bilateral extensor plantar responses The lower limb spasticity was much reduced when the patient lay down She could stand unsupported even with her eyes closed, but not without much swaying, if, when standing, she looked downwards or to the left, she immediately lost her balance

Her walking difficulty seemed to be due to loss of balance and lower-limb spasticity Both factors were much influenced by posture, and as signs of general cerebellar involvement were slight, drugs acting on the vestibular apparatus or the basal ganglia seemed worth trying Dimenhydrinate (Dramamine ') reduced frequency of micturition but gave no improvement in walking On benzhexol hydrochloride ('Artane) (2 mg q i d) she reported blurring of vision for small print but improved mobility

A double-blind controlled trial was carried out using benzhexol, ethopropazine hydrochloride (Lysivane) trifluoperazine ('Stelazine), and calcium lactate A week s supply of each drug, with dosage instructions, was given to the patient in a sealed lettered envelope The key was held by one of my partners, and the patient was told not to tell me the dose or colour of the tablets The benzhexol was given in tablets of a different dose (5 mg b d) to prevent its recognition The patient was given a chart to record daily her walking capacity, bladder control, general sense of wellbeing, and any side-effects attributed to the tablets She was seen at the end of each week's treatment She took benzhexol 2 mg q i d until the eve of the trial

Her first trial tablets proved to be calcium lactate Her performance became much worse and, after a fall on the second day, her husband forbade her to take any more tablets The second week, on ethopropazine, produced improvement, especially towards the end of the week, but in the third week, on trifluoperazine walking and mood deteriorated a change possibly exaggerated by anxiety over her son's interview for a grammar-school place In the fourth week, on benzhexol, her performance improved greatly Though still relying on the walls and furniture, she could take two to three steps unaided and could move round the house more rapidly None of the drugs had significant effect on bladder control

There seems little doubt that her walking was improved by benzhexol and, to a lesser extent, by ethopropazine Since the trial she has continued to take benzhexol (2 mg 3–4 hourly during the day) and the effect persists

London, N W 5

ANTHONY RYLE

PLACEBO EFFECT IN MENTAL NURSING

SIR,—The powerful therapeutic effect of placebos in general medicine is well known, and it has been shown[1] that chlorpromazine is only slightly more effective than placebos in chronic schizophrenia As the behaviour of chronic mental patients is greatly affected by their nurses' attitude it seemed useful to discover if this attitude, too, is affected by the nurses' beliefs about the drugs their patients are having

60 chronic female patients, 42 of them schizophrenic, who had been having an average daily dose of 210 mg chlorpromazine for many months, were randomly divided into two groups After a preliminary fortnight to establish a baseline, without any environmental changes, and to the knowledge of the pharmacist alone, group A was changed to placebo Three weeks later group B was also changed to placebo After a further week, when group A had been on placebo for a month, and group B for a week, the staff having believed them to be still on chlorpromazine, the nurses were told to administer a placebo, and a week later this was withdrawn and the patients knew themselves to be without medication

The patients' behaviour at different periods of the trial was assessed by nursing reports of such disturbances as aggression, restlessness, insomnia, or withdrawal

The number of reports of disturbed behaviour was

Trial week	*Group A* *Medication*	*Reports*	*Group B* *Medication*	*Reports*
1	Chlorpromazine	4	Chlorpromazine	8
2	Chlorpromazine	6	Chlorpromazine	6
3	Substituted dummy	5	Chlorpromazine	9
4	Substituted dummy	5	Chlorpromazine	5
5	Substituted dummy	4	Substituted dummy	4
6	Substituted dummy	4	Substituted dummy	9
7	Prescribed dummy	17	Prescribed dummy	23
8	None	18	None	27

And the reports of disturbance during different periods were

	Reports	*Patient-weeks*
Stabilised on chlorpromazine	42 in	200 (*21*)
On dummy unknown to patient or staff	27 in	150 (*17*)
On prescribed dummy	40 in	60 (*66*)
Chlorpromazine and dummy withdrawn	37 in	60 (*61*)

These results indicate that the (unknown) substitution of a placebo produced no deterioration, but that with the nurses told to use a placebo, reported disturbances increased threefold 6 patients were described as unmanageable, dramatic regressive behaviour was demonstrated and a return to chlorpromazine was requested, a further 4 patients were so described in

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1 Salisbury B J Hare E H *J ment Sci* 1957 103 53[illegible]

the last week without drugs No greater instability was manifested in group A, although this group was off chlorpromazine for longer than group B

It is clear that patients became more disturbed when nurses were aware of drug withdrawal So either there was a continued benefit after chlorpromazine withdrawal which was overridden by the effect of nurse anxiety, or the only action of the drug at any time was its placebo effect The results are not surprising as the sisters involved were uniformly of the opinion that the introduction of chlorpromazine had reduced the use of sedatives, E C T, and leucotomy and made easier the free management of patients But in one ward whose sister had predicted that no ill-results would follow withdrawal there was no rise in disturbances, while in another whose sister foretold a recurrence of aggression and destruction, and threatened to resign, disturbances rose from 1 to 17 a week

A placebo normally symbolises to the patient his doctor's care [2] In hospital it may also stand for the nurse as a protection against the patient's demands, and withdrawal of this protection may lead to emotional insecurity on both sides Tranquillity in the chronic mental patient may depend more on nursing than on tranquillisers

I am grateful to May & Baker Ltd , for the supply of blank pills, and to Miss I Lumb, hospital pharmacist, for her cooperation

Warlingham Park Hospital,
Surrey

M K LE VAY

A SIGN OF SURGICAL EMPHYSEMA

SIR,—The well-established courtesy of a spoken greeting from one's patient has a special diagnostic significance in a thoracic unit, it serves to indicate the presence of surgical emphysema arising from the chest far earlier than any other method of examination A peculiar nasal intonation is heard

Although loosely to be described as a "stuffy nose", only once has it been mistaken for this in several hundred observations, the note is somewhat flatter, and the patient is commonly unaware of the change in his speech For a number of years this sign has been infallibly noted and indicates the presence of surgical emphysema of even small degree not yet noted by the nursing staff Its only prerequisite is that the patient shall have been sitting up, the small areas of emphysema often noted in the region of thoracoscopy stabs were not associated with the sign since in such cases the patients were commonly nursed lying with the affected side uppermost Surgical emphysema in an upright patient has never been noted without this sign, which occurs long before the characteristic "bloated-face" appearance In most minor degrees of the condition, a certain training based on grosser experiences of it is necessary to recognise the faint change in voice

Only three mechanisms suggest themselves Venous obstruction, leading to turbinate congestion, is most unlikely, since it is not appreciated visibly, neither does the same voice appear in cases of recognised venous congestion or obstruction Lymphatic obstruction, due to tissue separation by air, to which the turbinates are unduly susceptible, cannot be refuted, but the most likely cause is that air simply rises in the tissue planes and causes a local congestion of both venules and lymphatics immediately around the turbinates In all cases, small "pockets" of surgical emphysema can be palpated at the root of the neck, provided the search be thorough, even though the amount there be slight and the maximum degree elsewhere

Modesty does not caution a claim for originality in the description of this bedside sign, since it is one of almost no clinical value!

King Edward VII
Memorial Chest Hospital,
Hertford Hill near Warwick

J C A RAISON

Parliament

Administration of Queen Mary's Hospital, Roehampton

AT the end of question time on Dec 12, Mr ENOCH POWELL, the Minister of Health, made the following statement

"With the agreement of the boards of governors of Queen Mary's Hospital, Roehampton, and of Westminster Hospital, I have decided, subject to consultation with London University, and to any necessary consultation with the Charity Commission by the Roehampton governors, to transfer the administration of Queen Mary's Hospital from my department to the board of governors of Westminster Hospital

"The separate identity of Roehampton will be maintained and war-pensioners will continue to have the same priority as at present I shall add to the Westminster board not less than three members representative of the Roehampton governors and of the ex-Service interests The governors and the ex-Service interests will also be substantially represented on the house committee of the hospital The services now provided by the Roehampton governors will, of course, not be affected, and the administration of the limb-fitting centre will remain the responsibility of my department

"The arrangements which I have announced will give the Roehampton governors and the ex-Service interests a direct share, which they have hitherto not had, in responsibility for running the hospital, and should guarantee the maintenance of its unique status"

Dr EDITH SUMMERSKILL While I have no objection to the Minister's statement, can he tell the House why it has been necessary to make this change?—Mr POWELL The proportion of ex-Service men occupying beds at Roehampton has been falling and is now only about a third of the total In these circumstances, it seemed right that new arrangements should be made if the unique status of the hospital and the priority of the ex-Serviceman were to be absolutely safeguarded

QUESTION TIME

Drug Prices

Lord BALNIEL asked the Minister whether he would make a statement on the renewal of the voluntary scheme for the regulation of drug prices —Mr POWELL replied Agreement has been reached with the Association of British Pharmaceutical Industry on a number of modifications to the scheme and it is to be renewed, as modified, until June 30, 1964 The main modifications, all of which should result in further restraint on prices, are as follows

(i) Provision is made for the prices of some widely used patented drugs to be negotiated directly

(ii) The percentage of sales that must be exported if the export price is to be the maximum price is increased from 20 to 25

(iii) The formula which fixes the maximum price for products which do not satisfy the export criterion, and for which there are no exact unbranded equivalents, is revised so as to result in lower maxima

(iv) The definition of new drugs, which are free from control during their first three years, is so revised as to exclude products which manifestly owe nothing to fresh research

I should like to acknowledge the cooperation of the Association in the discussions that have led to agreement on these modifications

R C P's New Building

Mr G JOHNSON SMITH asked the Minister of Housing and Local Government and Minister for Welsh Affairs whether the plans for the proposed new building for the headquarters of the Royal College of Physicians, on the east side of Regent's Park, had been approved by him —Mr HENRY BROOKE replied This proposal has been referred to me by the London County Council because it constitutes a departure from the approved development plan, in which this area is allocated for residential use It involves the demolition of Someries House, which was originally designed by Nash as an adult orphanage,

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2 Wolf, S Pinsky, R H *J Amer med Ass* 1954 155 339

but little remains of his design, it has been extensively altered and is now used as Government offices. In 1946 the Gorrell Committee reported that this building could and should be demolished. This view was accepted by the Crown Estate Commissioners, who decided to choose a skilled developer, advised by an architect, acceptable to them, to redevelop the site in harmony with the surrounding Nash buildings and terraces.

The scheme of redevelopment has been prepared by Messrs Denys Lasdun and Partners for the college. The Royal Fine Art Commission says that it is well satisfied with the design; it feels that it would be acceptable as a neighbour to the regency buildings which are to be preserved. The Crown Estate Commissioners have given their consent to the plans. It is intended that all the trees on the western boundary facing Regent's Park shall be retained. The St Pancras Borough Council has no objection, subject to questions of access, and the London County Council is disposed to grant planning permission. Before I authorise it to do so, I have arranged for a small model of the building and its setting to be exhibited for a week, so that Members may have the chance to see the design for this important proposed building and its relationship to the Nash terraces.

Strontium and Leukæmia

Mr R W SORENSEN asked the Minister of Health, as representing the Minister for Science, to what extent an increase in the presence of strontium and leukæmia had been detected in infants, children, young people and adults respectively during the past two years.—Mr POWELL replied: The average levels of strontium 90 measured in bone during 1959 as a whole show some increase on those recorded during 1958 for still-born infants, children, and young people, but there was relatively little change from the first to the second half of 1959. I regret I can only give figures for deaths from leukæmia. In the age-groups 0–4, 5–14, 15–24, and 25 upwards these were 141, 192, 95, and 1958 in 1958, and 152, 219, 124, and 2039 in 1959.

Mr SORENSEN: Is it not true that the figures for leukæmia show a serious increase?—Mr POWELL: The figures for leukæmia, unfortunately, have been on the increase for the past 30 or 40 years. There is no clear reason for connecting the two matters to which this question refers.

Hospital Underspending

Mr H J BOYDEN asked the Minister what amount of underspending he anticipated in the capital programme of the hospital authorities this financial year.—Mr POWELL replied: Returns earlier in the year showed some underspending but hospital boards were authorised to undertake additional works. I cannot anticipate the final outturn. Mr BOYDEN: Is it not rather deplorable that when the Government set out at last to improve the hospital service and increase the amount of hospital building they should, almost before it starts, be caught by underspending?—Mr POWELL: I am anxious to spend, if possible, every penny of my capital estimate, and I have, for example, in the Newcastle region authorised a further £500 000 of capital work.

Disinfestation of Aircraft

Mr F E NOEL-BAKER asked the Minister what steps he had taken to ensure that all aircraft were properly disinfected and cleared of flies and other insects before or on arrival at United Kingdom airports.—Miss EDITH PITT replied: All civil aircraft coming from countries outside the Western European Union and the Republic of Ireland must declare on landing when and where they were last disinfected and cleared of insects. The health authority then decides what further action to require on grounds of health. Mr NOEL-BAKER: Can the hon. Lady give a categorical assurance that the Word Health Organisation recommendations about aircraft disinfestation are being rigidly applied at all British airports? Further, is she satisfied with the procedure laid down by the W.H.O., and are we in fact taking advantage of the most up-to-date and effective insecticides which are available for this work?—Miss PITT: Past experience has shown that the risk of introducing infectious diseases into this country by aircraft is very small. Disinfecting or disinsecting on arrival in the United Kingdom is not normally necessary since in some circumstances—for example, in yellow-fever-infected areas—the international sanitary regulations require, among other sanitary measures, the disinfection or disinsecting of the aircraft before departure, and in any case no vector-borne quarantinable disease exists in this country and public-heath measures would prevent its spread were it introduced.

Home-helps

Mr N N DODDS asked the Minister, in view of the increasing practice of local authorities demanding payment for the provision of home-helps to those in receipt of National Assistance, what progress had been made in discussions with associations representing local health authorities to stop this practice, and what action he had taken to assist such people meanwhile.—Miss PITT replied: The Association of Municipal Corporations has now advised its members that it considers this practice unjustifiable; discussions with the County Councils Association are continuing. Meanwhile I understand that the National Assistance Board's officers use their discretionary powers where necessary to ensure that the payment of such a charge does not leave a recipient of assistance with less income than the National Assistance standard.

Social Workers

Mr KENNETH ROBINSON asked the Minister if he accepted the recommendation in the Younghusband report concerning financial assistance from central Government funds for the training of social workers, and when he intended to introduce the necessary legislation.—Mr POWELL replied: I consider that the present arrangements for financial assistance to trainees should be given a fair trial before further steps are contemplated. Mr ROBINSON: Is not the Minister aware that the Younghusband Working Party, which gave a good deal of thought to this matter, came to the exactly opposite conclusion and thought that the present arrangements would not be suitable for the expansion of training? Will he not give this matter further thought before reaching a final decision?—Mr POWELL: This is not a final decision. I am sure that at present the number of trainees is not limited by the absence of any Exchequer grant, and so it seems reasonable to see how the present arrangements work.

Mr G T SWINGLER asked the Minister what steps he was taking to increase the number of psychiatric social workers in the National Health Service. Miss PITT replied: Facilities for training have been provided at two further universities this year, but availability of experienced supervision remains the limiting factor and this can only improve gradually. Mr SWINGLER: Is the Parliamentary Secretary not aware of the desperately serious shortage in so many areas, which calls for the most urgent and drastic steps in schools and universities to recruit more people, and for the greatest effort on the part of those who are qualified to give the training?—Miss PITT: There is no shortage of applicants. As I indicated in my answer, part of the training is actual case-work—practical work—and that needs an already qualified psychiatric social worker in order to undertake the training of recruits to the service, but steps have been taken to improve the position.

Venereal Disease and Young People

Dr DONALD JOHNSON asked the Minister what steps he was taking to counteract the increased incidence of venereal disease amongst young people. Mr POWELL: Local health authorities, hospitals, and general practitioners were reminded last year of their responsibility to cooperate in efforts to reduce the incidence of venereal disease generally, but I am not satisfied that we yet understand sufficiently the significance or causes of the increase amongst young people, and I am considering how these can best be investigated. Dr JOHNSON: Does the Minister not agree that this is an extremely serious problem owing to the new drug-resistant strains of infection that are about, and while moral objugations in these days are unfortunately rather discounted, does he not consider it within his scope at least to emphasise the virtues of personal cleanliness, which have lapsed in so many instances at the same time as other virtues?—Mr POWELL: I am not sure that moral the last week without drugs No greater instability was manifested in group A, although this group was off chlorpromazine for longer than group B

It is clear that patients became more disturbed when nurses were aware of drug withdrawal So either there was a continued benefit after chlorpromazine withdrawal which was overriden by the effect of nurse anxiety, or the only action of the drug at any time was its placebo effect The results are not surprising as the sisters involved were uniformly of the opinion that the introduction of chlorpromazine had reduced the use of sedatives, E C T, and leucotomy and made easier the free management of patients But in one ward whose sister had predicted that no ill-results would follow withdrawal there was no rise in disturbances, while in another whose sister foretold a recurrence of aggression and destruction, and threatened to resign, disturbances rose from 1 to 17 a week

A placebo normally symbolises to the patient his doctor's care[2] In hospital it may also stand for the nurse as a protection against the patient's demands, and withdrawal of this protection may lead to emotional insecurity on both sides Tranquillity in the chronic mental patient may depend more on nursing than on tranquillisers

I am grateful to May & Baker Ltd , for the supply of blank pills, and to Miss I Lumb, hospital pharmacist, for her cooperation

Warlingham Park Hospital,
Surrey

M K LE VAY

A SIGN OF SURGICAL EMPHYSEMA

SIR,—The well-established courtesy of a spoken greeting from one's patient has a special diagnostic significance in a thoracic unit, it serves to indicate the presence of surgical emphysema arising from the chest far earlier than any other method of examination A peculiar nasal intonation is heard

Although loosely to be described as a " stuffy nose ", only once has it been mistaken for this in several hundred observations, the note is somewhat flatter, and the patient is commonly unaware of the change in his speech For a number of years this sign has been infallibly noted and indicates the presence of surgical emphysema of even small degree not yet noted by the nursing staff Its only prerequisite is that the patient shall have been sitting up, the small areas of emphysema often noted in the region of thoracoscopy stabs were not associated with the sign since in such cases the patients were commonly nursed lying with the affected side uppermost Surgical emphysema in an upright patient has never been noted without this sign, which occurs long before the characteristic " bloated-face " appearance In most minor degrees of the condition, a certain training based on grosser experiences of it is necessary to recognise the faint change in voice

Only three mechanisms suggest themselves Venous obstruction, leading to turbinate congestion, is most unlikely, since it is not appreciated visibly, neither does the same voice appear in cases of recognised venous congestion or obstruction Lymphatic obstruction, due to tissue separation by air, to which the turbinates are unduly susceptible, cannot be refuted, but the most likely cause is that air simply rises in the tissue planes and causes a local congestion of both venules and lymphatics immediately around the turbinates In all cases, small " pockets " of surgical emphysema can be palpated at the root of the neck, provided the search be thorough, even though the amount there be slight and the maximum degree elsewhere

Modesty does not caution a claim for originality in the description of this bedside sign, since it is one of almost no clinical value!

King Edward VII
Memorial Chest Hospital,
Hertford Hill near Warwick

J C A RAISON

---

[2] Wolf, S , Pinsky, R H *J Amer med Ass* 1954, 155 339

Parliament

Administration of Queen Mary's Hospital, Roehampton

AT the end of question time on Dec 12, Mr ENOCH POWELL, the Minister of Health, made the following statement

" With the agreement of the boards of governors of Queen Mary's Hospital, Roehampton, and of Westminster Hospital, I have decided, subject to consultation with London University, and to any necessary consultation with the Charity Commission by the Roehampton governors, to transfer the administration of Queen Mary's Hospital from my department to the board of governors of Westminster Hospital

" The separate identity of Roehampton will be maintained and war-pensioners will continue to have the same priority as at present I shall add to the Westminster board not less than three members representative of the Roehampton governors and of the ex-Service interests The governors and the ex-Service interests will also be substantially represented on the house committee of the hospital The services now provided by the Roehampton governors will, of course, not be affected, and the administration of the limb-fitting centre will remain the responsibility of my department

" The arrangements which I have announced will give the Roehampton governors and the ex-Service interests a direct share, which they have hitherto not had, in responsibility for running the hospital, and should guarantee the maintenance of its unique status "

Dr EDITH SUMMERSKILL While I have no objection to the Minister's statement, can he tell the House why it has been necessary to make this change ?—Mr POWELL The proportion of ex-Service men occupying beds at Roehampton has been falling and is now only about a third of the total In these circumstances, it seemed right that new arrangements should be made if the unique status of the hospital and the priority of the ex-Serviceman were to be absolutely safeguarded

QUESTION TIME

Drug Prices

Lord BALNIEL asked the Minister whether he would make a statement on the renewal of the voluntary scheme for the regulation of drug prices —Mr POWELL replied Agreement has been reached with the Association of British Pharmaceutical Industry on a number of modifications to the scheme and it is to be renewed, as modified, until June 30, 1964 The main modifications, all of which should result in further restraint on prices, are as follows

(i) Provision is made for the prices of some widely used patented drugs to be negotiated directly

(ii) The percentage of sales that must be exported if the export price is to be the maximum price is increased from 20 to 25

(iii) The formula which fixes the maximum price for products which do not satisfy the export criterion, and for which there are no exact unbranded equivalents, is revised so as to result in lower maxima

(iv) The definition of new drugs, which are free from control during their first three years, is so revised as to exclude products which manifestly owe nothing to fresh research

I should like to acknowledge the cooperation of the Association in the discussions that have led to agreement on these modifications

R C P 's New Building

Mr G JOHNSON SMITH asked the Minister of Housing and Local Government and Minister for Welsh Affairs whether the plans for the proposed new building for the headquarters of the Royal College of Physicians, on the east side of Regent's Park, had been approved by him —Mr HENRY BROOKE replied This proposal has been referred to me by the London County Council because it constitutes a departure from the approved development plan, in which this area is allocated for residential use It involves the demolition of Someries House, which was originally designed by Nash as an adult orphanage, Mr Roy married Beatrice Anne, daughter of Henry Barstow She survives him with two sons and a daughter

SERGEI TERNOVSKY

M D

Professor Ternovsky, who was chief of pædiatric surgery in the Second Moscow Medical Institute (the Institute), Pirogov died on Nov 19 His book on the surgery of childhood, based on his lectures for students at the institute, first published in 1949, has become a standard textbook in Russia and is now in its third edition His chief surgical interests were renal disease, including calculi and ectopia vesicæ, congenital abnormalities of the alimentary tract, and bone and joint surgery, especially osteitis He was made a member of the Academy of Medical Sciences in recognition of his work, and had lately been elected a member of the British Association of Pædiatric Surgeons

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" A charming and cultured man in his early sixties, Professor Ternovsky has been a notable figure at pædiatric surgical meetings in eastern Europe over the past few years His quiet, constructive, and critical contributions to discussion were the more welcome because of the patently friendly, and often humorous, vein in which they were given He spoke French and German well and had a far greater command of English than he cared to admit, so that in a cosmopolitan crowd his wide interests found a ready and sympathetic response He will be greatly missed at a time when his integrity and ability made him an outstanding, if unofficial, ambassador of his country Pædiatric surgery has lost a brilliant technician, a wise doctor, and a kind man "

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" Dr Bignold was a quiet, modest man with a keen sense of humour, in which there was a vein of gentle cynicism It must be confessed that those whose ideas or actions were subjected to his amused probing did not always relish this attention, but his qualities were given full recognition by Ayr County Council, which, with his advice, gained in medical matters a reputation for being progressive second to none in Scotland Probably he himself regarded the early success of his diphtheria immunisation campaign as his greatest personal contribution to public health, but maternity and child welfare and the school medical and dental services all received direct and practical encouragement from him He was a leader in the experiment of appointing whole-time clinical specialists to work in local-authority areas An obstetrician was appointed in 1937 and later a chest physician and a pædiatrician It ill behoves one of these specialists to speak of the success of these appointments, though this has been commented on elsewhere Suffice it to say that when the National Health Service was in the planning phase, one at least of the whole-time specialists viewed with apprehension the discontinuance of a working association which had been satisfying professionally, and which on the personal side had been happy, respectful, and even affectionate

" Dr Bignold's happy home life was appreciated by those fortunate enough to be admitted to his personal friendship His wife only survived him for a few days and died on Dec 12 They leave a general practitioner son, and a daughter now a sister at the Ayrshire Central Hospital, itself a memorial to her father's vision and skilled planning "

Major-General D C. MONRO

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" Monro started the field surgical units to deal with the long lines of communication in the advance of the 8th Army to Tunisia, and he has been called the ' Father ' of these units, which is very true These small units moved forward with the advancing troops and were able to give surgical treatment to many of the wounded at a very early stage He also developed the Tobruk plaster splint which was used in the evacuation of lower-limb fractures with great success Jock Monro was a great character He was an excellent surgeon and one of the neatest operators I have ever seen He was a first-class administrator He knew all the surgeons in the Middle East Force and was trusted and respected by everyone He was good at most games, first-class at golf, and an enthusiastic small-boat sailor He had a great fund of humour, and was excellent company It is a sad thought that we shall not meet Jock again "

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The Hospital for Sick Children, Great Ormond Street, London

Capps F P A M.B Lond , D OBST house physician

Gilchrist G S M B Glasg house physician

Gupta J S M.S Lucknow, F.R C.S D O.M.S part time M O ophthalmic department obligations come within the scope of my department, but I am sure that all those concerned understand the importance of emphasising the right rules upon all those with whom they come in contact

Family Planning Poster

In answer to a question asking if the Government approved of the action of the British Transport Commission in ordering the removal of a perfectly harmless Family Planning Association advertisement, Lord CHESHAM replied My Lords, I am told that the poster was withdrawn by the British Transport Commission because it was controversial on religious grounds The responsibility for such decisions rests with the Commission, and the Government do not seek to influence or express any opinion on them

Lord SHEPHERD My Lords, is it not remarkable that this advertisement, which had no controversial or objectionable matter in it, which had been fully accepted by the Board four or five months ago, and which was issued by a very responsible organisation, should now be removed, bearing in mind that dubious advertisements are still being shown on the railways in London? Does the noble Lord not remember that a similar attempt was made in this House to prevent the Family Planning Association from appealing for funds on the B B C, and on that occasion the Board of the B B C stood firm? Is it not against all tolerance that this should happen, and is it not more an arrogant attack on liberty?

Lord CHESHAM My Lords, I do not believe this is an arrogant attack on liberty at all So far as I am aware no-one has suggested—at least, I have not been told so—that this poster was in any way offensive in itself The poster itself is not exceptionable, but I am informed by the British Transport Commission that they have received letters objecting to the poster on religious grounds I think I should remind the noble Lord of Rule 18 of the Commission's regulations regarding advertisements which they cannot accept Rule 18 deals with posters

> "which refer to religious or sacred subjects in a manner which might give offence or contain matter or illustrations likely to be construed as religiously controversial"

Evidently this poster was so considered, and the British Transport Commission, it appears, saw fit to withdraw it on those grounds

Charge for Road Casualties

Lord STONHAM asked the Government if they would abolish the obligation which rests on hospitals to collect an emergency treatment fee of 12*s* 6*d* in respect of persons who require treatment as the result of a road traffic accident Lord NEWTON replied My Lords, hospital authorities are entitled to these fees and they therefore have a duty to claim them Any changes in the obligation imposed on vehicle users by the Road Traffic Act to pay these fees on a claim being made would require legislation, and this is a matter which the Minister of Health will bear in mind at the appropriate time Lord STONHAM My Lords, whilst I welcome the information that this matter is being borne in mind, may I ask whether the noble Lord is aware that the cost to hospitals of collecting this fee is very considerably more than 12*s* 6*d*, that it involves a great deal of work for the police, and that the motorist, who has to pay it, thinks it grossly unfair, because often he is not responsible for the accident This imposition is unfair, it costs more than we receive, and it would be in the interests of the Treasury to abolish it Lord NEWTON My Lord, perhaps I should be summarising the views of the noble Lord if I were to say that he regards this fee as anomalous in a great many ways If that is so it has been anomalous for a long time, because this provision for payment of a fee dates from 1934 There was an opportunity to abolish it, as the noble Lord would like, during the passage of the National Health Service Act in 1946, but it was not abolished, and in fact the provision was actually continued in the tenth schedule to that Act I am not promising that, when the appropriate time comes, my right honourable friend will do what the noble Lord wants, on the other hand, I am not shutting the door on that

Lord STONHAM asked the Government whether, in view of the great amount of work falling on hospital staffs from the present system of collecting from insurance companies treatment charges in respect of persons injured in road accidents, they would negotiate an agreement with the companies whereby they pay to Her Majesty's Treasury a lump sum based on premium income, which would be the estimated equivalent of the present sums they pay for the treatment of injured persons in hospital —Lord NEWTON replied My Lords, as the Road Traffic Act, 1960, specifies who should make, and who should receive, these payments it would be necessary to amend the Act to make legal any other method of collection But the Minister of Health will bear in mind, at the appropriate time, the noble Lord's suggestion Lord STONHAM When it is being considered, will the noble Lord have regard to the fact that the average recovered in any one year from all these charges is about a third of a million pounds—it was £350,000 last year—and that, in view of the great cost to hospitals, and the tremendous time it takes to agree these claims with the insurance companies, we should be making a great bargain if we got a quarter of a million pounds from them?—Lord NEWTON My Lords, I am sure my right honourable friend will bear that point in mind also

Obituary

DONALD WHATLEY ROY

M A, M B Cantab, F R C S, F R C O G

Mr Donald Roy, consulting obstetric surgeon to St George's Hospital, London, died at York on Dec 9 at the age of 79

He was born at Appleton Roebuck, York, and his father, the Rev James Roy, was the rector of Stockton-on-Forest From St Peter's School, York, he went to Sidney Sussex College, Cambridge, as an exhibitioner and scholar He took first-class honours in both parts of the natural sciences tripos and at St George's Hospital he won the university scholarship and the Brodie prize for clinical surgery After qualifying in 1906 he held resident appointments at the General Lying-in Hospital, York Road, at the Royal Free Hospital, and at George's where he became in due course obstetric tutor and registrar In 1913 he was appointed to the staff of the Samaritan Hospital for Women During the 1914–18 war he served at first as a surgeon in the R N V R with the Grand Fleet In 1917 he transferred to the R A M C, and from 1917 to 1918 he was in charge of the surgical division of the Northamptonshire War Hospital Soon after his return to civilian practice he joined the staff of George's He was an examiner for the Universities of Cambridge and London, the Royal Colleges, and the Society of Apothecaries For some time he was a member of the University's Board of Advanced Studies and of the London Hospitals Representative Committee Earlier he was consulting obstetrician to the London County Council hospitals His published work included articles on the teaching and organisation of midwifery and contributions to several textbooks He was elected F R C O G in 1929

C M G writes

"To those who worked with him, Dr Roy was a great man His intense devotion to detail will always be remembered by them as the outward and visible evidence of the integrity that they came so wholeheartedly to respect and admire His basic ideas of pelvic surgery were ahead of his time and it is regrettable that his active life did not last sufficiently long for him to see their general acceptance As an operator, he strove for an almost inhuman perfection, sparing none of his assistants, and still less himself As a teacher, he was more revered in retrospect than at the actual moment of instruction and this was largely due to his disarming modesty The courage with which he faced the physical disasters of his middle age roused the wonder of those who knew it, and it is greatly to be regretted that he was never given the recognition that his great qualities deserved"

Mr Roy married Beatrice Anne, daughter of Henry Barstow She survives him with two sons and a daughter

SERGEI TERNOVSKY
M.D

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The Hospital for Sick Children, Great Ormond Street, London

Capps, F P A M.B Lond D OBST house physician.

Gilchrist G S , M B Glasg house-physician

Gupta J S M.S Lucknow F.R C.S D O M S part time M O ophthalmic department

News

University of Oxford

On Dec 10 the following degrees were conferred

D M—R M Bannerman

B M—I G McGill, T N Miller, D H Myers, T H D Arie, J B P Stephenson Peter Husband, G E G Sladen, Chester White, W J Appleyard, Gerassimos Spyros Spathis, J E Cawdery, J S Smith, T S Low Beer, H P Berg D P G Bolton, R G Hett R A L Sutton, J W Baker, J B Wood, R V Clements, L R C Bain, J R W Christie Brown, T W Meade, Charles Rowlatt, J M Gumpel, M A Lee, C E Taylar, A K McKinlay, S H Milton, H M B Busfield, Anne M Waring, Sylvia N Clayton, Gillian R Sutton, Pamela F Hull, Anne C Maddocks, Gillian M Roberts, Elizabeth J E Neale, J L Nicholas, D L Wingate, John Kenwright, S R Meadow, J S Meyrick, John Millward (in absentia)

University of London

Dr M D Milne, lecturer at the Postgraduate Medical School of London, has been appointed to the chair of medicine at Westminster Medical School

Dr Milne, who is 45 years of age, graduated B SC from the University of Manchester in 1936 and M B three years later From 1940 to 1945 he served with the 8th Army in field units In 1946 he returned to Manchester and was house-physician and registrar at the Royal Infirmary In 1950 he was appointed lecturer in medicine at Manchester University, and he proceeded to the degree of M D the following year He took up his present appointment at Hammersmith in 1952 He was elected F R C P in 1958 His published work *has dealt mainly with renal disease and disorders of metabolism*

The title of professor of oral medicine has been conferred on Dr R V Bradlaw in respect of his post at the Institute of Dental Surgery, of professor of biophysics as applied to medicine on Dr L F Lamerton in respect of his post at the Institute of Cancer Research Royal Cancer Hospital, of professor of occupational psychology on Mr Alec Rodger in respect of his post at Birkbeck College, and of professor of physical anthropology on Dr N A Barnicot in respect of his post at University College

University of Aberdeen

On Dec 14 the following degrees were conferred

M D—Eleanor M Adams (with commendation)

M B, Ch B—M L G Addison, Alan Bremner, G M Bruce, D S Gill, Gordon Jamieson, Roy Mercer, Audrey F Stewart, Mary M Sutherland

University of Edinburgh

The university court is to administer as a trust fund the J J M Shaw Cancer Research Fund (Cancer Control Organisation for Edinburgh and South-East Scotland) of about £30,000 The capital and income of the fund are to be applied at the discretion of the university for research into the causes and treatment of malignant disease and, in particular, to provide fellowships or travelling scholarships

Dr Bruce Mackay has been appointed to a lectureship in anatomy, and Dr R G S Leask to a lectureship in clinical chemistry

Royal College of Physicians of London

Dr Louis Forman will deliver a Watson Smith lecture on Tuesday, Jan 10, at 5 P M, at the college, *Pall Mall East*, S W 1 He will speak on the reaction of the skin to certain metals

British Institute of Radiology

The annual congress of this institute will be held from April 26 to 28 at Church House and Central Hall, London, S W 1

Wanted in the Congo

The World Health Organisation is urgently seeking to recruit more staff, all of whom must speak fluent French, for the health services in the Congo

There are over 100 vacancies for physicians, surgeons, anæsthetists, microbiologists, public-health officers, pharmacists, radiographers, and field and laboratory technicians at salaries ranging from $3600 to $7300 The candidates are being recruited by W H O on the assumption that they may after a suitable period be offered long-term contracts by the Congolese Government All interested should write for full details to the regional director, W H O, 8, Scherfigsvej, Copenhagen, Ø, Denmark

London Jewish Hospital Medical Society

A meeting of this society will be held on Thursday, I
at 8 15 P M, at 11, Chandos Street, London, W 1, wl
C O Carter will speak on Advice to Parents on Geneti

Society for Psychosomatic Research

This society is offering a prize of £50, given by
Halley Stewart trust, for original observations on a
somatic theme studied in patients seen in general p
Entries should be sent to the secretary, 96, Portlanc
London, 1, by Dec 1, 1961

British Occupational Hygiene Society

A meeting on health physics is to be held by this soc
Wednesday, Jan 4, at 10 A M, at the London Scl
Hygiene, Keppel Street, London, W C 1 In the n
there will be a discussion on personal radiation dose m
ments and in the afternoon on environmental measure
Further particulars may be had from the hon publicity
Dr J S McLintock, Medical Service, National Coal
Hobart House, London, S W 1

Medical Academy in Singapore

This body, which specialists in all branches of
medicine set up in Singapore in 1958 under the title
Academy of Physicians and Surgeons, has changed its n
Academy of Medicine The office-bearers for 1960–61

Master, Mr D W C Gawne, assistant master, Dr G
Leng, scribe, Dr Ho Yuen (General Hospital, Singapore, 3),
Dr N C Sen Gupta, bedel, Mr J A Jansen, censors, Prof
Ransome, Prof G S Yeoh, Mr D R Gunn, Dr Khoo Oo
Mr Y Cohen

Institute of Diseases of the Chest, London

Clinical demonstrations for doctors will be arrang
Dr K M Citron on *Fridays from Jan 13 to March 24*
lectures will be given on Wednesdays from Jan 11 to Ma
by Sir Russell Brock, Dr N Lloyd Rusby, Mr W P C
Dr F P Lee Lander, Mr J R Belcher, Dr E H H
Dr J H Scadding, Mr L L Bromley, Dr R V C
Mr Donald Barlow, and Dr Lynne Reid All the le
will be held at 5 P M at the institute, Brompton Ho
Fulham Road, S W 3

New Headquarters for W H O

Representatives of the Swiss Confederation, the Re
and Canton of Geneva, and the World Health Organisat
Dec 5 signed formal agreements concerning the constr
of the new headquarters building for W H O in Genev

The agreements provide for an interest-free loan of 20
Swiss francs granted by the Confederation, and another
million Swiss francs at a nominal interest granted by the S
Geneva The site, known as " Chautagnes ', is in the comm
Pregny-Chambésy M Jean Tschumi, professor of archi
at the École Polytechnique de Lausanne, has designed th
ten-storey building, which is to cover an area of 16,425 sq
is to have a "curtain' façade composed of glass walls with alum
sunbreak elements on a framework of reinforced concrete c
with marble

A meeting of the medical group of the Royal Photographic
of Great Britain will be held on Thursday, Jan 5, at 7 I
16, Princes Gate, London, S W 7, when Mr Charles Engel a
John Brace will speak on closed-circuit television in medical dia
research, and teaching

CORRIGENDUM *Anticoagulant Therapy*—An error is conta
the opening of our account (Dec 3, p 1247) of this symp
Dr R P Biggs said that the coumarin anticoagulant drugs
fall in the blood-level of factor VII (*not* VIII), IX, and X

Births, Marriages, Deaths

BIRTHS

WILEY—On Nov 22, at the Western Hospital, Toronto, to Pamela, Dr A M Wiley—a son

The Lancet · Saturday 31 December 1960

HUMORAL CHANGES IN ARTERIOSCLEROSIS

VESTIGATIONS ON LIPIDS, FATTY ACIDS, ETONE BODIES, PYRUVIC ACID, LACTIC ACID, AND GLUCOSE IN THE BLOOD

W Schrade
M D Frankfurt
PROFESSOR OF MEDICINE

E Boehle
M D Frankfurt
CLINICAL ASSISTANT

R Biegler
M D Frankfurt
CLINICAL ASSISTANT

E FIRST MEDICAL CLINIC, UNIVERSITY OF FRANKFURT-ON-MAIN

Investigations of the humoral changes in arterio-lerosis have been almost entirely restricted to the rious lipid substances, but the increase of lipids in the ood is only a part of a complex humoral syndrome

Methods and Cases

We made these investigations and estimations

(1) Total lipids by extraction with alcohol/ether (3/1), dissolving the extract in chloroform, drying and weighing,) total and free cholesterol (Schmidt-Thome and Augustin 42), (3) lipid phosphorus (Allen 1940), (4) acetone, aceto-etic acid, β-oxybutyric acid (Engfeldt 1920, modified by teigerwald 1960), (5) pyruvic and lactic acid using spectro-otometric technique (Warburg and Christian 1937), (6) olyenoic acids, spectrophotometrically, after isomerisation by kali (Herb and Riemenschneider 1953), and (7) fatty acids by as chromatography (James and Martin 1952), both in the tal fatty acids and in the fatty acids of the individual lipid actions

Separation of the phospholipids from the total lipid fraction y dialysis using the technique of van Beers et al (1958), paration of unesterified fatty acids with ‘ Amberlite IRA 45 ’ Biegler et al 1960), fractionation of the cholesterol esters nd glycerides by adsorption chromatography on sicilic acid

In the spectrophotometric estimation of polyenoic acids, tty-acid concentrations which gave absorption maxima for vo , three-, and four-fold unsaturated fatty acids were lected Since the optimum isomerisation conditions differ for e various polyenoic acids, it is not feasible to estimate the ofold to six-fold unsaturated fatty acids in a single estimation

Calculation of significance was carried out by Student's t ”-distribution When P was less than 0 05, the differences ere regarded as significant

ases Studied

Male ambulatory patients with arteriosclerosis were xamined One series also included a few women (table V)

Arteriosclerosis ” was diagnosed if the patients had xperienced either a myocardial infarction or a cerebral ttack, or had suffered from angina pectoris or a sclerosis f the peripheral arteries The diagnosis was supported y clinical, X-ray, electrocardiographic, oscillographic, nd angiographic examinations The control subjects ere men under observation—one series also included a ew women (table V)—or members of the staff of the ospital who after a complete examination were free from ny illness (particularly of the circulatory system), or any isturbance of metabolism Patients and controls were natched according to age-groups

The different body-types were classified according to Kretschmer's nomenclature (Kretschmer 1951), and by Burkhardt's index (Burkhardt 1939)—

$$I = \frac{\text{body length}^3}{\text{weight} \times 100}$$

Persons with an index under 700 were designated athletic-pyknic (mesomorphic) Indices under 550 characterised pyknics (endomorphs), leptosomatics (ecto-morphs) had values over 900 No particular type could be assigned to persons with indices between 700 and 900

Patients and controls received the usual hospital diet No special dietetic arrangements were made before the examinations were performed The blood-samples were taken before breakfast, after an overnight fast of twelve to fourteen hours As there is an almost invariable fall of blood-lipids after myocardial infarction, analyses in these cases were not carried out until the lapse of at least seven weeks from the acute episode

Results

THE LIPID CONTENT OF THE BLOOD

Fig 1 is based on 452 male cases of arteriosclerosis, and shows the mean values of total cholesterol, free cholesterol, phospholipids, and (calculated) glycerides 60 healthy men of approximately the same age (40 to 60) served as controls In the patients with arteriosclerosis, the glycerides were the most raised of the lipid fractions The increase of the total cholesterol and of phospholipids is approximately the same, and is relatively slight The distinctly greater rise of glycerides, compared with that of cholesterol and phospholipids, was also demonstrated in another series, in which the glycerides were not calculated but were estimated by absorption chromatography The fasting serum of patients with arteriosclerosis is often slightly turbid as a result of the increased glycerides

The intensity and frequency of hyperlipidæmia differed with the type of arteriosclerosis and with the vascular territory in which the changes were principally localised (table I)

Hyperlipidæmia was greatest in patients with coronary disease (321), and least in those with cerebral sclerosis (71) Cases with predominantly peripheral disease (60) were intermediate 70% of the total number of patients had

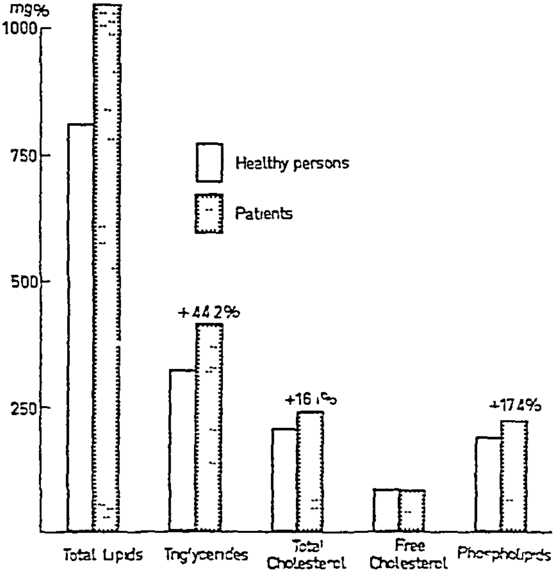

Fig 1—Lipid content of the blood in 452 arteriosclerotic and 60 healthy subjects Mean values (Mg % = mg per 100 ml.)

TABLE I—THE BLOOD-LIPIDS IN HEALTHY PERSONS AND PATIENTS WITH DIFFERENT LOCALISATION OF ARTERIOSCLEROSIS
(Mean and standard error of the mean)

—	Number of cases	Total lipids (mg per 100 ml)	Total cholesterol (mg per 100 ml)	Free cholesterol (mg per 100 ml)	Phospholipids (mg per 100 ml)	Glycerides (mg per 100 ml)
Healthy persons (16–60 years of age)	60	809±12.8	205±4.9	79±2.7	190±4.7	324±9.1
Myocardial infarction	171	1090±20.6	240±9.7	79±5.4	224±8.8	508±14.5
Angina pectoris	73	1070±24.1	213±11.2	79±7.2	226±9.4	481±17.2
Coronary and cerebral arteriosclerosis	33	1082±25.2	213±9.7	78±8.1	229±8.4	490±18.3
Coronary and peripheral arteriosclerosis	35	1068±25.5	249±8.7	78±6.5	227±9.3	467±17.1
Coronary cerebral and peripheral arteriosclerosis	6	1301±39.2	261±13.4	95±9.4	237±9.1	680±24.3
Coronary sclerosis (total)	321	1086±21.5	213±10.1	79±7.6	226±9.0	497±17.7
Cerebral sclerosis	71	931±15.2	227±8.5	72±1.9	218±7.7	376±11.2
Peripheral arteriosclerosis	60	969±16.3	232±8.8	75±6.0	214±8.1	408±12.0
Arteriosclerosis (total)	152	1017±16.6	239±7.1	77±4.3	223±7.9	466±12.1

hyperlipidæmia, while the lipid values in the blood of the other 29% lay within normal limits. Of the 321 cases of coronary sclerosis, 80% showed an increase of blood-lipids, but only 46.5% of cases of cerebral sclerosis showed such a change. Among 60 cases of peripheral sclerosis, 60% showed an increase of blood-lipids (Boehle et al 1958).

The different levels and varying frequency of hyperlipidæmia in the three groups are associated with the different bodily build and age-groups—among other factors—of patients with coronary, cerebral, and peripheral sclerosis. Of 321 persons with coronary disease, 66% were of pyknic or pykno-athletic type, 31% with relatively featureless body-type, and only 1.8% were leptosomes. On the other hand, in patients with the cerebral sclerosis, those with a relatively non-characteristic build or of leptosomatic type were predominant. 46% had an index between 700 and 900, 6% above 900. Of the cases of peripheral sclerosis, only 33% belonged to the pyknic or pykno-athletic group, the majority (60%) were uncharacteristic, while 7% were distinctly leptosomatic.

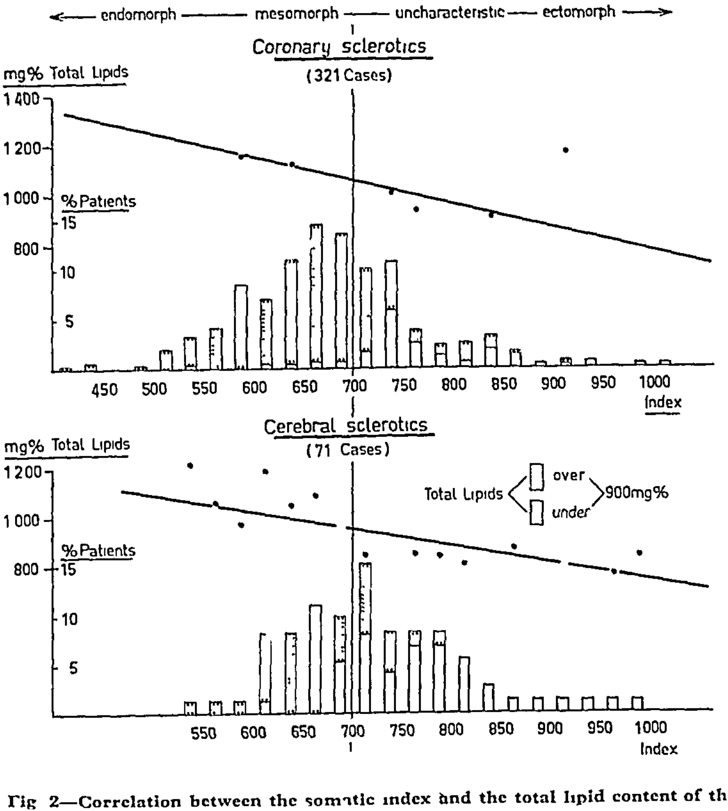

Fig 2—Correlation between the somatic index and the total lipid content of the blood in 231 patients with coronary sclerosis.

There is a negative correlation between the somatic index and the total lipids (fig 2). This was statistically demonstrated in the coronary and cerebral sclerosis groups. In peripheral sclerosis, the coefficient of correlation (−0.34) was slightly below the statistical coincidence value (−0.37). It follows that, in arteriosclerosis, the greater the body-bulk, the higher is the blood-lipid level. A second significant factor is age. The majority of cases of cerebral sclerosis (63%) were over 60 (indeed, almost half of them were over 70), whereas patients under 60 formed the majority (75%) of cases of coronary sclerosis, the largest proportion (63%) being between 45 and 60. This age-distribution partly explains the fact that the mean values of blood-lipids in coronary sclerosis are higher than in cerebral sclerosis, because the age-trend of blood-lipids usually reaches its maximum in the sixth decade and because, after 60, the mean values for blood-lipids tend to fall.

THE FATTY ACIDS OF THE BLOOD

Since all blood-lipid fractions, except the free cholesterol, contain fatty acids, there arises the question of their behaviour in association with hyperlipidæmia in arteriosclerosis. Such investigations appear to be of particular importance because it is known that the fatty-acid content of the diet greatly influences the lipid level in the blood. We have investigated a large number of arteriosclerotic patients and normal persons by analysing the total fatty acids of the serum—both spectrophotometrically, after isomerisation with alkali, and by gas chromatography. In a third series, spectrophotometric estimations of polyenoic acids, and in a fourth series gas-chromatographic analyses of the fatty acids of the various lipid fractions, were undertaken.

Spectrophotometric Estimation of Polyenoic Acids in the Total Fatty Acids of the Serum

Table II presents the mean values found in 100 male arteriosclerotics with hyperlipidæmia, and those of 85 healthy male subjects with normolipidæmia. The total fatty acids were 59.2% higher in the arteriosclerotics than in the control group, but the polyenoic acids played little or no part in this increase.

The serum in the arteriosclerotics showed a slight rise of linoleic and a slight decrease of arachidonic acid, but the differences from the control group were not significant. It follows, therefore, that the increase of total fatty acids in arteriosclerotics is caused by the non-essential fatty acids—i.e., the saturated and

TABLE II—THE POLYENOIC ACIDS IN THE BLOOD OF HEALTHY AND ARTERIOSCLEROTIC SUBJECTS
(Mean and standard error of the mean)

Group	Age	No	Total lipid (mg. per 100 ml. serum)	Total fatty acid (mg. per 100 ml. serum)	Dienoic		Trienoic		Tetraenoic	
					(mg. per 100 ml. serum)	(percentage of total fatty acids)	(mg. per 100 ml. serum)	(percentage of total fatty acids)	(mg. per 100 ml. serum)	(percentage of total fatty acids)
I Healthy	20–30	23	708±20·0	314±16·2	66·4±3·1	21·1±0·9	9·1±1·3	2·9±0·5	12·6±0·7	4·0±0·2
	31–40	20	734±18·3	330±12·8	69·0±2·9	20·9±0·6	9·9±1·6	3·0±0·7	11·2±0·9	3·9±0·2
	41–50	16	768±20·4	356±13·6	72·5±3·9	20·3±0·8	10·3±1·4	2·9±0·4	13·2±0·8	3·7±0·4
	51–60	20	778±24·2	364±16·4	74·5±2·9	20·2±0·9	11·6±1·4	3·2±0·5	12·7±0·8	3·5±0·3
	61–70	6	770±38·0	378±22·4	74·4±5·2	19·7±1·7	11·7±2·0	3·1±0·8	12·5±0·9	3·3±0·7
All cases		85	762±20·2	355±14·2	72·5±3·0	20·4±0·9	10·6±1·4	3·0±0·6	13·1±0·8	3·7±0·3
II Arteriosclerotic	<40	2	1310±26·8	648±13·1	96·5±2·9	14·9±0·2	20·8±1·4	3·2±0·2	12·3±0·6	1·9±0·08
	41–50	31	1215±49·9	626±22·0	88·2±5·2	14·1±0·7	16·2±2·9	2·6±0·4	11·3±0·8	1·8±0·16
	51–60	43	1100±43·7	524±20·4	76·4±4·6	14·6±0·5	15·2±2·7	2·9±0·5	11·0±1·1	2·1±0·13
	61–70	24	1086±52·0	510±28·6	80·6±5·1	15·8±0·8	15·3±2·6	3·0±0·4	10·2±1·2	2·0±0·19
All cases		100	1185±48·2	565±22·6	83·6+4·8	14·8+0·6	16·3+2·7	2·9+0·4	11·3+1·0	2·0+0·16
Difference as a percentage between I and II			+55·2	+59·2	+15·5	−27·5	+53·8	−3·3	−13·5	−46·0

the monounsaturated acids. Accordingly, the increased lipids circulating in the blood of arteriosclerotic patients with hyperlipidæmia have a different composition from those in the controls. In the arteriosclerotics, the linoleic acid formed 14·8% of the total fatty acids in the blood, whereas in the normals it was 20·4%. This difference is significant (t=5·1, P= >0·001). The percentages of linolenic acid in the two groups are not definitely different, but the proportion of arachidonic acid is significantly reduced in the arteriosclerotic group (t=4·85, P= >0·001).

As shown in table II, the total lipid and the total fatty-acid content of the blood rises with increasing age in the examined controls. The proportions of linoleic and arachidonic acids in the total fatty acids decrease slightly. The differences in the proportions of the polyenoic acids between the healthy and the arteriosclerotic subjects are significant also in corresponding age-groups (t=5·0, P= >0·001).

Gas-chromatographic Investigation of the Total Fatty Acids in Serum

Two further series, one of 34 normal men and one of 42 arteriosclerotic men, were investigated. The total serum-lipids in the normals varied between 628 and 962 mg. per 100 ml. (mean 805 mg.), the total fatty acids between 287 and 503 mg. (mean 393 mg.). Among the arteriosclerotics, 32 showed hyperlipidæmia with a total lipid content between 933 and 1830 mg. (mean 1195 mg.), and total fatty acids between 453 and 1007 mg. (mean 608 mg.). In the 10 arteriosclerotics with unconfirmed hyperlipidæmia, the mean value of the serum-lipids was 847 mg. (734–987 mg.), and of the total fatty-acid content 393 mg. (317–437 mg.).

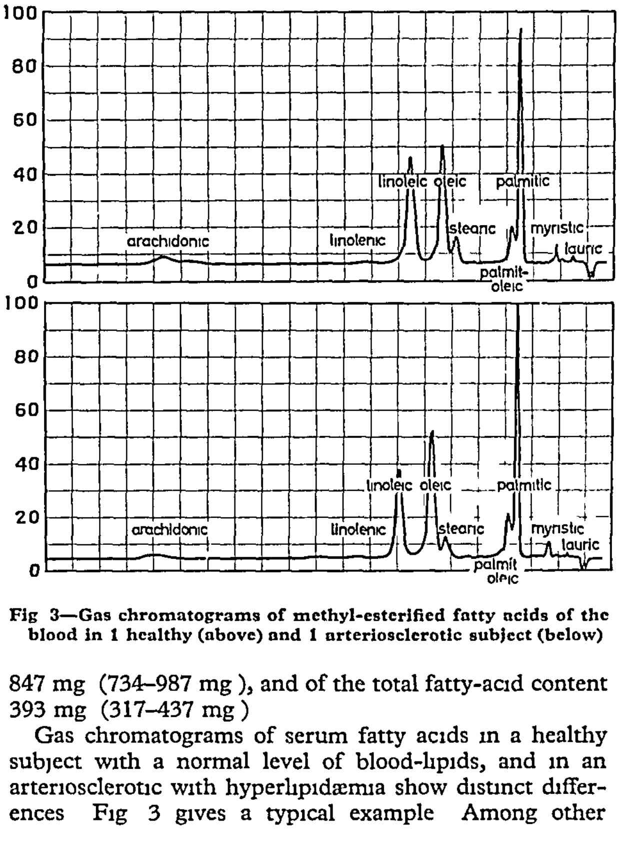

Fig. 3—Gas chromatograms of methyl-esterified fatty acids of the blood in 1 healthy (above) and 1 arteriosclerotic subject (below).

Gas chromatograms of serum fatty acids in a healthy subject with a normal level of blood-lipids, and in an arteriosclerotic with hyperlipidæmia show distinct differences. Fig. 3 gives a typical example. Among other

TABLE III—COMPOSITION OF THE SERUM FATTY ACIDS IN HEALTHY AND ARTERIOSCLEROTIC PATIENTS WITH AND WITHOUT HYPERLIPIDÆMIA (Mean and standard error of the mean)

Group	Age	Mean age	Number of cases	Total fatty acids (mg. per 100 ml.)	Percentage of total fatty acids							
					Myristic	Palmitic	Palmitoleic	Stearic	Oleic	Linoleic	Arachidonic	Remaining
Healthy	<30	23	10	385±20	1·43±0·15	27·75±0·58	6·67±0·96	6·70±0·76	25·10±1·21	24·35±1·28	5·12±0·51	2·88±0·23
	31–40	36	4	400±14	1·53±0·15	26·72±1·36	5·78±0·42	6·44±0·42	27·20±1·09	23·13±1·97	5·48±0·79	3·72±0·28
	41–50	46	5	382±26	1·44±0·13	27·17±1·71	6·76±0·77	6·36±0·56	24·39±1·81	23·91±2·34	6·72±1·39	3·25±0·16
	51–60	56	9	396±17	1·16±0·13	27·50±0·96	7·00±1·09	6·68±0·82	26·77±0·59	22·85±1·17	4·97±0·54	3·07±0·21
	61–70	68	6	408±30	1·85±0·27	27·38±0·92	7·73±0·92	5·72±0·95	25·72±1·10	22·64±1·09	5·46±0·44	3·50±0·47
	All cases	44	34	393±19	1·45±0·09	27·41±0·43	6·86±0·44	6·44±0·36	25·79±0·51	23·45±0·65	5·41±0·31	3·19±0·22
Patients with hyperlipidæmia	41–50	45	3	651±122	1·92±0·66	32·58±0·69	10·83±0·41	5·15±0·19	25·63±1·03	18·09±0·63	2·32±0·12	3·48±0·31
	51–60	57	17	581±22	1·50±0·16	31·37±0·81	8·25±0·53	6·39±0·46	28·96±0·71	17·38±0·70	2·82±0·32	3·33±0·32
	61–70	64	9	653±61	1·36±0·15	32·35±1·26	8·74±0·57	5·28±0·41	28·54±1·43	18·08±1·50	2·74±0·62	2·91±0·72
	>70	74	3	578±53	1·80±0·18	31·26±2·17	5·34±0·72	9·56±2·19	23·39±0·98	18·97±2·52	3·13±0·34	6·58±3·28
	All cases	56	32	608±41	1·53±0·11	32·06±0·58	8·36±0·39	6·26±0·34	28·01±0·61	17·79±0·57	2·77±0·23	3·22±0·95
Patients without hyperlipæmia	41–50	48	4	381±23	1·91±0·49	28·12±1·14	9·49±1·18	4·90±0·27	26·98±0·73	22·03±2·23	3·22±0·46	3·35±0·85
	51–60	56	4	387±21	0·97±0·29	31·63±1·05	8·02±0·86	5·42±0·35	27·41±1·34	19·62±1·45	4·30±0·59	2·63±0·20
	>60	69	2	429±9	1·22±0·18	29·16±2·14	6·53±2·06	5·82±0·69	28·00±1·73	21·21±0·51	4·25±1·20	3·81±0·83
	All cases	55	10	393±17	1·39±0·26	29·73±0·83	8·31±0·72	5·29±0·23	27·35±0·63	20·90±1·07	3·86±0·38	3·17±0·51

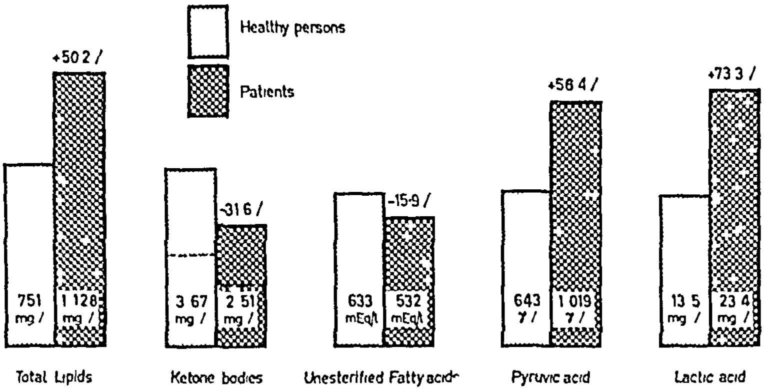

Fig 5—Content of ketone bodies, pyruvic acid, and lactic acid in the blood of 100 healthy subjects and 100 arteriosclerotics Mean values (γ% = μg per 100 ml)

applies to the acetone, acetoacetic acid and β-oxybutyric acid The control-group mean value for pyruvic acid was 643 μg (±28 7), and in the arteriosclerotics, 1019 μg (±56 1) This increase of 58 4% is significant (t=5 62, P= >0 001), as is that of lactic acid in the arteriosclerotics 23 4 mg (±1 3) was the mean in the patients, as compared with 13 5 mg (±1 1) in the controls (t=5 83, P= >0 001)

INVESTIGATION OF CARBOHYDRATE TOLERANCE

Double glucose-loading tests were carried out on 192 non-diabetic arteriosclerotics, and on 52 control subjects (Boehle and Schrade 1960) In 108 of the former (56 3%) the result was abnormal (fig 6) The blood-sugar reaction was normal in 84 cases (43 7%) In 35 of the arteriosclerotics, there was slight glycosuria during the loading test

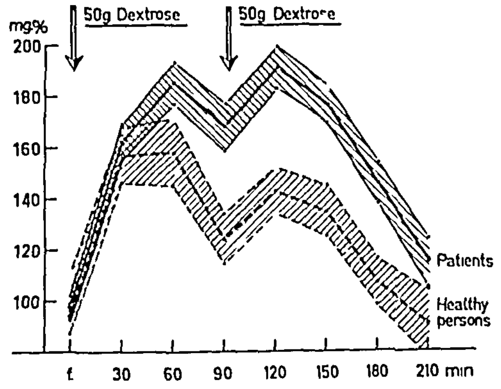

Fig 6—Blood-sugar curves after glucose-loading tests in healthy and arteriosclerotic subjects (Mean values and scatter)

This latent disturbance of carbohydrate metabolism was most frequent in patients with myocardial infarction, of 74 cases in this group, 73% showed an abnormal response to loading On the other hand, only 40% of the 38 cases of cerebral and 35 cases of peripheral sclerosis showed reduced sugar-tolerance

Fig 7 shows that a normal blood-sugar response was commoner than an abnormal one in the younger patients In the age-group 46 to 50, the number with a normal and with a pathological response was about equal Above the age of 50, the proportion of patients with decreased sugar-tolerance increased, and in the eighth decade, practically all patients had an abnormal tolerance

Fig 8 shows the relation between the results of sugar-loading and the constitutional type of the patient With few exceptions, leptosomatics with arteriosclerosis had normal sugar-tolerance, but with a decreased index—i e , with increasing body-weight, abnormal tolerance curves became more frequent All patients with pyknic characteristics had a decreased tolerance

Fig 9 shows that underweight arteriosclerotics had abnormal blood-sugar curves much less frequently than those who were overweight The blood-sugar curve was always abnormal if there was gross overweight With two exceptions, it was found that the frequency of abnormal tolerance curves increased the greater the degree of hyperlipidæmia With more than 1400 mg per 100 ml total blood-lipids all patients presented abnormal sugar-tolerance curves (fig 10)

Our results show that, in arteriosclerosis, abnormal sugar-tolerance curves are often found in those of pyknic-athletic (mesomorphic) or pyknic (endomorphic) build, especially when there is a tendency to corpulence

It also appears that there is a similar relation between abnormal sugar-tolerance and hyperlipidæmia The correlation between disturbance of carbohydrate metabolism and age is less close

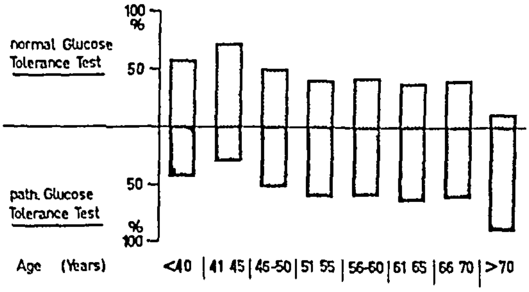

Fig 7—Relation between response to sugar-loading and age in arteriosclerosis

These relations may explain that decreased carbohydrate-tolerance is most frequent in patients with myocardial infarction, in this group, the majority were between the ages of 50 and 60 and were either of pykno-athletic or of pyknic build and also had hyperlipidæmia

In other groups also, the probability of finding a decreased sugar-tolerance was greater (1) the older the patient, (2) the more striking the pyknic or pykno-athletic features, and (3) the higher the level of blood-lipids It was found that abnormal tolerance curves could, however, occur in patients with diametrically different characteristics—i e , those of the asthenic-leptosomic type, underweight, and with low blood-lipids

It must be indicated that the sugar-loading tests in patients with myocardial infarction, described here, were

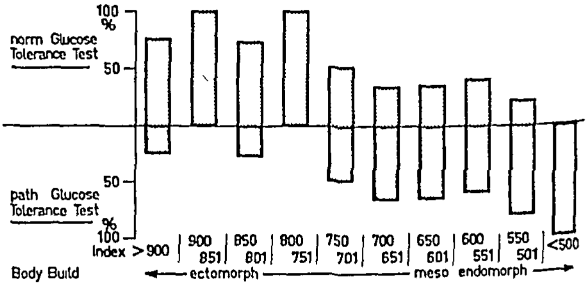

Fig 8—Relation between response to sugar-loading and constitutional type in arteriosclerosis

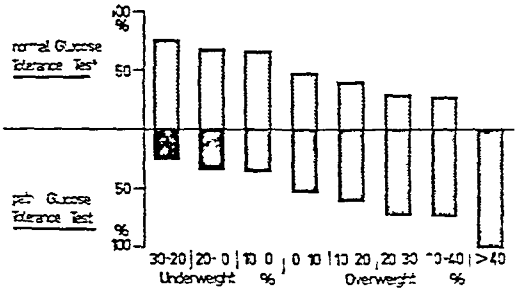

Fig 9—Relation between response to sugar-loading and body-weight in arteriosclerosis

carried out not earlier than seven to eight weeks after the acute episode, because we found that in the first days after the infarction, and occasionally after a cerebral attack, the carbohydrate metabolism was usually temporarily disturbed

Discussion

Our investigations show that biochemical abnormalities, affecting various fields of metabolism, occur in patients with arteriosclerosis Apart from lipoproteins, which are not considered here, blood-lipids are most commonly altered Of these, the triglycerides of the serum show the greatest increase, while the increase of cholesterol and of phospholipids is distinctly less (Hauss and Boehle 1955, Boehle et al. 1958, Schrade et al 1959) Albrink and Man (1959) have recently found an increase of triglycerides in arteriosclerosis

The composition of the fatty acids of the serum-lipids is characteristically changed in cases of arteriosclerosis with hyperlipidæmia The increase in the total fatty acids of the serum is caused almost entirely by an increase of saturated and monoenoic acids there is only a slight rise of linoleic acid Arachidonic acid is likely to be reduced

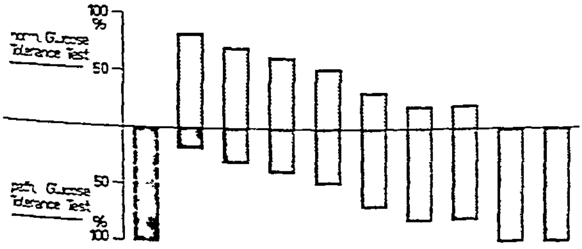

Fig 10—Relation between response to sugar-loading and lipid content of the blood in arteriosclerosis

Our spectrophotometric and gas-chromatographic observations gave identical results The total lipid extract in arteriosclerosis with hyperlipidæmia is richer in non-essential fatty acids and poorer in essential ones than is the case in health

This shift in the spectrum of the total fatty acids partly depends on the great increase of triglycerides, which are predominantly composed of non-essential fatty acids In addition to this “ dilution effect ”, there is also a pathological composition of the individual lipid fractions

In hyperlipidæmia, the extra fatty acids of the elevated cholesterol esters and phospholipids are largely saturated, and monounsaturated, and only to a lesser extent polyenoic acids

In one series of examinations, a decreased proportion of arachidonic acid was found (by spectrophotometry) in the fatty acids of the glycerides of the arteriosclerotic patients Antonis and Bersohn (1960) also stated that there was a diminution of the proportion of all polyenoic acids in the triglycerides of patients with ischæmic heart disease (by spectrophotometry)

Our results coincide with those of Lewis (1958), but differ from those of James et al (1957)

Spectrophotometrically, Lewis found less linoleic acid in the cholesterol esters of 12 cases of myocardial infarction than in healthy subjects On the other hand James et al, using gas chromatography, did not detect any difference between the linoleic-acid content in either the acetone-soluble or the acetone-unsoluble fraction of the plasma-lipids in 12 coronary cases and in 12 normal cases It should be noted that James only investigated patients with no increase of cholesterol and glycerides in the plasma, whereas we have found that, as a general rule, the proportions of fatty acids are only changed in cases of arteriosclerosis that are accompanied by hyperlipidæmia. Furthermore, the values for linoleic acid (12·1 or 12·4%) in the acetone-soluble fraction, given by James et al (1957), are remarkably low This acetone-soluble fraction contains the triglycerides (with a linoleic-acid content of about 10%), but it also contains the cholesterol esters which have a distinctly higher content of linoleic acid

The changes demonstrated in the fatty-acid components of the blood-lipids cannot be regarded as being specific, because we have found similar ones in other examples of hyperlipidæmia, especially in diabetes, while similar but less striking changes occur in myxœdema and in the nephrotic syndrome (Schrade et al 1959) The hyperlipidæmia of arteriosclerosis does, however, differ from the other endogenous types, as it is, at least to some extent, affected by nutritive factors

If one bears in mind the fact that, in arteriosclerosis, the blood contains an excess of non-essential fatty acids and that there is a relative (not a true) deficit of essential fatty acids, the known effects of various food fats on the blood-lipids become comprehensible

The hyperlipidæmia of arteriosclerosis is connected with the variations of the intermediate products of fat catabolism and of glycolysis in the blood In blood, taken under the same conditions as those required for estimation of basal metabolism, the ketone bodies are reduced, and the pyruvic and lactic acids are raised in arteriosclerosis with hyperlipidæmia It must be emphasised that none of the patients showed signs of circulatory decompensation or of liver disease It should be mentioned that oral administration of 62·5 g of butter to arteriosclerotic subjects did not lead to a rise of ketone bodies, or, in comparison with the controls, only to a greatly delayed increase After oral administration of two doses, each of 50 g of dextrose, the pyruvic acid and lactic acid rose much higher than in the controls The participation of carbohydrate metabolism is also shown by the frequency of an abnormal blood-sugar curve after double loading with glucose It must be added that Kohn and Prozan (1959) have recently demonstrated a high level of uric acid in the blood in arteriosclerosis (Gertler et al 1951) Finally, it should be remembered that the glucoproteins of the serum may be altered in arteriosclerosis (Antonini 1954, Voigt and Schrader 1955 Schwartz and Gilmore 1958)

The hyperlipidæmia of arteriosclerosis forms only a part of a general humoral syndrome There is obviously a complex disturbance of the regulatory mechanism which normally maintains a normal level in the blood of lipids, lipoproteins and glucoproteins, glucose, and various other products of intermediate metabolism—perhaps also, of uric acid This regulatory mechanism normally decreases in efficiency with advancing age the lipids increase, and the lipoprotein and glucoprotein spectra undergo changes, while carbohydrate-tolerance diminishes, although not to the same extent in both sexes or in all people It is possible that hereditary factors, constitution, and mode of nutrition (which may also be indicative of the constitutional type) are significant in this respect Many investigators have shown that, as a general rule, pyknic or athleto-pyknic people have a higher blood-lipid level than have those of slightly asthenic or leptosomic build It may well be that the factors of age and constitution explain why the humoral changes are most often encountered in cases of coronary sclerosis and least often in association with cerebral sclerosis, because, as we have demonstrated, among male coronary cases, between the ages of 50 and 60, pyknics or athleto-pyknics predominated, whereas among those with cerebral sclerosis there were more older people of uncharacteristic or slender build

The fact that in arteriosclerosis, there may be complex disturbances of metabolism, which have a direct correlation with age, constitution, and nutritional state, indicates that the humoral syndrome is an independent phenomenon, not primarily connected with arteriosclerosis The observation that there is no parallelism between the type and extent of the vascular disease on the one hand, and the intensity of the changes in the blood on the other, has the same significance There are cases of extreme arteriosclerosis, even with a pronounced atheromatous character, in which the blood is normal Conversely, there may be well-marked blood changes in cases of slight and not extensive arteriosclerosis It cannot be doubted that humoral changes are not a necessary prerequisite for the development of arteriosclerosis It is, however, highly probable that they further the development of this disease

Summary

Estimation of lipids in 452 cases of arteriosclerosis showed that the triglycerides in the blood are increased to a greater extent than cholesterol and phospholipids

Hyperlipidæmia was seen most in 71% of cases with coronary disease, in 60% of those with peripheral sclerosis, but in only 46 5 cases of cerebral sclerosis

The different frequency of hyperlipidæmia in the three groups is associated (among other factors) with the fact that the bodily build and age-group of the coronary cases were different from those with cerebral sclerosis

Spectrophotometric estimations on the serum of 100 cases of arteriosclerosis, and gas-chromatographic analyses of 42 others, demonstrated a distinct increase in the proportions of saturated and monounsaturated fatty acids In arteriosclerosis accompanied by hyperlipidæmia, the serum-fat contains less linoleic and arachidonic acids than in health

In hyperlipidæmia, the extra fatty acids of the elevated cholesterol esters and phospholipids are largely saturated and monounsaturated, and only to a lesser extent polyenoic acids

In 100 arteriosclerotics with hyperlipidæmia, it was found that the ketone bodies were decreased in the fasting blood, whereas pyruvic and lactic acids were increased

In 192 non-diabetic arteriosclerotics, 56% showed diminished sugar-tolerance by the double-loading technique There was a direct correlation between the disturbance of sugar-tolerance and blood-lipids, but a less close relation to the age of the patients

The investigations indicate that hyperlipidæmia in arteriosclerosis forms part of a complex humoral syndrome, affecting a variety of metabolic processes

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PREDNISOLONE AND TESTOSTERONE PROPIONATE IN CIRRHOSIS OF THE LIVER

A CONTROLLED TRIAL

RONALD WELLS
M B B Sc , Lond , M R C P , D T M & H
LATE MEDICAL REGISTRAR,
DEPARTMENT OF MEDICINE, GENERAL HOSPITAL, SINGAPORE

THERE is no generally accepted comprehensive therapeutic regime for cirrhosis of the liver This is not surprising, because the progress of individual cases of cirrhosis is unpredictable, and, in the absence of dramatically successful methods, only extensive controlled trials can distinguish between responses to treatment and fortuitous recoveries Such trials are difficult to organise in cirrhosis, and personal bias may affect the results

The Patients

In 1957, favourable reports from France of corticoid therapy for cirrhosis (Cachin et al 1957, Fraisse et al 1957a and b, Girard et al 1957, Lamache et al 1957) and a study from Rome of testosterone propionate treatment for cirrhosis (Girolami 1953, 1956a and b) suggested an investigation in Singapore, where severe portal cirrhosis and postnecrotic cirrhosis are relatively common A clinical trial was organised and was continued until late 1959 A personal bias in favour of the prednisolone and testosterone treatments did develop during the trial, but all patients were managed strictly in accordance with a predetermined scheme, and because of language difficulties there was little direct mental contact with the patients

All patients admitted during the first sixteen months of the trial period to one of the male medical wards at the Singapore General Hospital with the initial diagnosis of cirrhosis were allocated to one of three series (control, prednisolone, testosterone) Some of these patients were suspected of having carcinoma of liver as well as cirrhosis, but it is sometimes difficult to distinguish carcinoma from benign nodular hyperplasia of the liver, and so all these patients were included in the trial with a view to rejecting them later if the diagnosis of carcinoma could be confirmed quickly Of 97 patients initially included, 17 were rejected within the first few days The diagnosis

TABLE I—RANDOMISATION CHECKS ON INITIAL CLINICAL DATA, AND FINAL DIAGNOSTIC CLASSIFICATION

—	Control series	Prednisolone series	Testosterone series
Total number of cases	27	27	26
Portal cirrhosis	21	22	23
Postnecrotic cirrhosis	5	4	3
Biliary cirrhosis	1	1	0
History of malnutrition (with opium addiction)	7 (6)	7 (6)	9 (6)
History of alcoholism	8	9	10
History of viral hepatitis	3	1	3
Extrahepatic biliary obstruction	1	1	0
Evidence of liver-cell failure	23	24	25
Evidence of portal hypertension	19	19	20
Mean initial age (yr.)	51·40	51·10	[illegible]
Mean initial serum-albumin (g. per 100 ml.)	2·84	2·72	2·67
Mean initial serum-gamma-globulin (g. per 100 ml.)	2·42	2·69	2·56
Mean initial thymol turbidity (units)	4·63	5·41	5·38
Mean initial bromsulphalein retention (normal <0·05 mg per 100 ml.)	0·25	0·29	0·33

of cirrhosis of the liver was confirmed in the remaining 80. Liver biopsy was done on all the patients, except 3 who were moribund on admission. A final classification was made in accordance with the report on classification of cirrhosis by Sherlock et al. (1956).

The first 15 of the 97 patients were allocated to one of the three series in rotation. But this method was open to bias when two or more cases presented simultaneously. So envelopes were prepared containing allocation instructions; these were sealed, shuffled and serially numbered. Each new patient, after the 15th, was first given a serial number and his series allocation was then determined by opening the appropriate envelope. At the conclusion of the trial analysis of the classification data and a number of randomisation checks showed the three series to have been initially substantially similar (table I). In this series, 18 out of 23 patients with a history of malnutrition were opium addicts.

Standard Investigations and Therapeutic Regimes

All patients not in coma had a standard series of investigations.

These included a hæmoglobin estimation, white-cell, reticulocyte, and platelet counts, erythrocyte-sedimentation rate, serum-proteins by electrophoresis, thymol turbidity, serum-bilirubin and alkaline phosphatase, bromsulphalein excretion, liver biopsy, and an X-ray of the chest. If the patient survived, barium-swallow and barium-meal X-ray examinations were done within a few weeks of inclusion in the trial. Records were kept of the size of liver and spleen, the abdominal girth and the body-weight. The hæmatological and liver-function tests were repeated at intervals during the trial.

All patients in the control, prednisolone, and testosterone series, who were not in prehepatic coma, were given a basic therapeutic regime.

They had a full normal hospital diet, but, if this was not eaten, they were given instead a 3000 calorie liquid diet, containing 80 g of protein, by intragastric drip. When discharged and treated as outpatients, they were encouraged to eat as much protein as possible. Throughout the whole period of the trial they received a daily oral vitamin supplement containing aneurine (thiamine) 38 mg, riboflavine 9 mg, pyridoxine 3 mg, nicotinamide 60 mg, folic acid 10 mg, ascorbic acid 300 mg, and 1500 units of vitamin D. They also received an initial injection of 1000 µg of vitamin B_{12}, with a further 1000 µg every three months.

Patients who were opium addicts usually continued to take their own opium or were given their full requirements. No attempt was made to reduce their opium in hospital or as outpatients, unless they themselves suggested it, as opium withdrawal seems to be particularly dangerous in the presence of severe cirrhosis. All the alcoholics were strongly advised to give up alcohol; about half of them ignored this advice.

If severe œdema or ascites was present, the patients were given 2 or 3 g of chlorothiazide and a similar amount of potassium chloride daily. Abdominal paracentesis to relieve ascites was avoided if possible and was rarely required. There were no incidents of hepatic coma that could be related to the administration of chlorothiazide. A single injection of 30 mg of menaphthone (vitamin K) was given if the one-stage prothrombin-time was more than 120% of normal before liver biopsy. Prehepatic and hepatic coma were treated by non-protein feeding, daily administration of 25 g of sodium glutamate intravenously, 2 g of tetracycline daily, and careful control of electrolyte balance. Gastrointestinal hæmorrhage was treated conservatively by blood-transfusion, and by the administration of 2 g of tetracycline daily until melæna ceased.

All patients in the prednisolone series were given an initial four-week course of 20 mg of prednisolone daily, and then, beginning with the seventh week, were given one week's prednisolone therapy at the same dosage every four weeks. In addition to the prednisolone, these patients were given 40 units of a long-acting corticotrophin preparation every fortnight.

All patients in the testosterone series were given injections of 100 mg of testosterone propionate on alternate days for the first four weeks, and thereafter 300 mg every fortnight.

Results

Follow-up

All surviving patients were treated in hospital until fit for discharge and for outpatient treatment. Some patients relapsed after discharge and were readmitted during the course of the trial. The initial period of admission averaged thirty-seven days for the patients in the control series, thirty-eight days in the prednisolone series, and thirty-one days in the testosterone series. The minimum follow-up was fourteen weeks and the maximum, up to the conclusion of the trial, was eighty-six weeks. After discharge, some of the patients did not attend for their follow-up appointments. Whenever an attendance was missed the patient was visited by the almoner next day, and most surviving patients became regular attenders. By purposely giving patients one or two too many or too few vitamin tablets it was possible to check if they took medicines regularly, and it is thought that most of them did.

Mortality

The mortalities in the three groups of patients and the immediate causes of death are summarised in table II.

15 patients died in hospital in hepatic coma and a further 6 died at home apparently in coma. 1 of the 3 in the prednisolone series who died in coma moved out of Singapore after fifteen weeks' treatment and had a total of only six weeks' further treatment during the next thirty-three weeks before death. Of the 6 testosterone-treated patients dying in coma, 1 had four weeks' treatment, another had eight weeks, and a third was treated for nine weeks; these 3 also had further treatment for various reasons, and died fourteen, twenty, and nineteen weeks later.

TABLE II—MORTALITIES AND IMMEDIATE CAUSE OF DEATH IN THE THREE TRIAL SERIES

—	Control series (27 cases)	Prednisolone series (27 cases)	Testosterone series (26 cases)
Death in hepatic coma	12	3	6
Death from [illegible]	2		0
Other deaths	1	3	2
Total	15	[illegible]	8

The 3 patients dying from hæmatemesis were all known to have œsophageal varices. Of the 6 dying from other causes 1 in the control series with biliary cirrhosis died soon after admission and was found to have multiple cholangitic abscesses, another in the prednisolone series died from pulmonary embolism associated with thrombosis of leg veins, a patient in the testosterone series died from pulmonary œdema, and another died in hyperpyrexia associated with an aseptic lymphocytic meningitis. The cause of death of 2 patients in the prednisolone series was unknown, 1 of them, after four and a half weeks' treatment, refused further therapy, and died thirty weeks later.

Liver-function Tests

In all three series, with few exceptions, the results of the liver-function tests varied with the clinical state. In the control series, the initial bromsulphalein excretion seemed to be more closely related to the prognosis than did any other of the investigations done. The relationships between mortality in the three series and the initial values for serum-albumin, serum-gammaglobulin, and bromsulphalein excretion are partially analysed in table III. This table also shows the changes seen during the trial between the first and last estimations of serum-albumin, serum-gammaglobulin, and bromsulphalein excretion in those patients with significantly abnormal values. Some of the patients in the prednisolone and testosterone series showed steady improvement in their liver-function tests while receiving regular treatment in the trial, but later died after failing to attend the clinic for varying periods.

Detailed analysis of the liver-function tests during treatment in the control, prednisolone, and testosterone series showed that the serum-proteins improved quicker in the prednisolone patients than in those receiving testosterone, but that the improvement in bromsulphalein excretion was greater in the testosterone series.

Additional Observations

A patient in the prednisolone series had a large gastric ulcer which did not respond to medical treatment, prednisolone was stopped, and a partial gastrectomy done. The patient was still alive and well at the end of the trial, but the prednisolone treatment must be regarded as a failure.

4 of the 5 control patients with postnecrotic cirrhosis died, but there were no deaths among the 7 postnecrotic cirrhotics in the prednisolone and testosterone series.

TABLE III—CHANGES IN THREE TESTS OF LIVER FUNCTION, AND RELATION BETWEEN MORTALITY AND INITIAL TEST RESULTS IN THE THREE SERIES

—	Control series	Prednisolone series	Testosterone series
Initial serum albumin			
>2·5 g per 100 ml —			
Total cases	16	14	14
Deaths	6	2	1
<2·5 g per 100 ml —			
Total cases	11	13	12
Deaths	9	5	7
Cases with increasing albumin	3	12	10
Cases with decreasing albumin	6	0	0
Initial serum gammaglobulin			
<2·5 g per 100 ml —			
Total cases	15	10	12
Deaths	7	1	1
>2·5 g per 100 ml —			
Total cases	12	17	14
Deaths	8	6	7
Cases with increasing globulin	4	1	1
Cases with decreasing globulin	7	14	12
Initial bromsulphalein retention			
<1·5 mg per 100 ml —			
Total cases	11	11	7
Deaths	2	1	1
>1·5 mg per 100 ml —			
Total cases	15	15	17
Deaths	12	5	5
Cases with increasing retention	10	3	0
Cases with decreasing retention	3	8	16

An analysis of follow-up notes shows that patients in the prednisolone series received more diuretic therapy than those in the control and testosterone series. This agrees with the clinical impression that the patients in the prednisolone series tended to have more œdema and ascites during the trial than the control and testosterone cases. In contrast, the records of liver size show that there appeared to be considerably greater increase in liver size in the patients in the testosterone series during the trial than in the control and prednisolone cases.

In fact, 2 of the patients receiving testosterone were suspected of having carcinoma of the liver, with enlarging firm, tender hepatic masses. But both these patients progressed well and were still alive over two years later, which suggests that the liver masses were large benign hyperplastic nodules.

The morbidity of cirrhosis is difficult to assess, but 4 of the controls, 14 of the prednisolone patients, and 13 in the testosterone series were certified fit for work.

Nearly all the patients were impotent when first seen, but 9 of those receiving testosterone volunteered that their libido and potency had returned during treatment. None of the control or prednisolone patients reported any return of libido.

Prednisolone, in the doses used, appeared to have little effect on the hæmatological manifestations of hypersplenism.

With the exception of the patient who had a gastric ulcer during prednisolone therapy, none of the patients in the prednisolone and testosterone series showed unwelcome side-effects.

Discussion

In Singapore, my experience with Patek's regime for cirrhosis (Patek 1937, Patek and Post 1941) has been generally disappointing, and, indeed, Patek's own results were not impressive (Patek et al. 1948). His 386 " control " cases, drawn from the records of five hospitals for 1920–40, received no special attention and had a 39% one-year survival, while his 124 test cases were transferred to a special unit, during a ten-year period up to 1948, where they received enthusiastic attention, had a 65% one-year survival. Alcoholism was reported in 77% of the test cases and in 54% of the controls, and 73% of the test cases had antecedent malnutrition as against only 17% recorded in controls. Alcoholic cirrhosis has a relatively good prognosis if the patients can be persuaded to give up alcohol, and, if a dietary and vitamin treatment has any value in the management of cirrhosis, it is likely to be most evident in undernourished patients. The enthusiastic management of Patek's test cases may have been important in reducing mortality, particularly among the alcoholics. The only 4 patients in the control series of the Singapore trial who showed evidence of substantial and sustained improvement all had severe antecedent malnourishment, and 2 of them were also alcoholics.

Androgen therapy has been used in the treatment of cirrhosis.

In 1938, Hall and Korenchevsky reported that the administration of a number of androgens—including testosterone propionate—resulted in enlargement of the liver of castrated rats, and they suggested that this might have a practical therapeutic significance in human liver disease. Testosterone propionate was also shown to increase the liver size in growing dogs (Blackman et al. 1944). Rosenak et al. (1947) reviewed the changes in cirrhosis which seem to be caused by excess œstrogens, and reported the results of treating 12 alcoholic patients, who had cirrhosis, with large doses of testosterone propionate

They concluded that there was some evidence of improvement and that testosterone propionate was a valuable adjunct Kinsell (1948) reported 2 patients with chronic hepatitis following acute viral hepatitis, who improved on 50 mg daily of testosterone, though other regimes had failed, and Rosenak et al (1950) mentioned another 6 cases of cirrhosis, all of whom improved on testosterone therapy Girolami has reported good results in 30 out of 50 cases of severe cirrhosis (1958), and, except for the possibility of producing prostatic hypertrophy, the treatment appears to have no serious contraindications in men.

The Singapore trial confirms that the administration of large doses of testosterone propionate in severe cirrhosis of the liver reduces mortality and morbidity, and brings about the return of serum-proteins and other tests of liver function to normal 6 women with severe portal cirrhosis were also treated in Singapore with large doses of testosterone propionate The results were generally good, although all developed mild hirsutism, and 4 had transient acneform eruptions Other male cirrhotics in Singapore have been treated with large doses of testosterone œnanthate, which appears to be preferable to testosterone propionate for maintenance therapy because of its longer action Experimental evidence in animals, and records of liver size during the controlled trial, suggest that the beneficial action of testosterone propionate in cirrhosis may be related to increased liver-cell regeneration

During the past decade, corticoid therapy for cirrhosis has been investigated in many centres, first with adrenal cortex (Webster 1950), cortisone (Hanger and Collins 1950), and then with prednisone and prednisolone

Prednisone therapy for cirrhosis is now widely used in France, though it has not been accepted elsewhere as standard practice It has been reported to exert an immediate strong diuretic effect in cirrhosis (Vachon et al 1956), with a related decrease in the urinary output of aldosterone (Vesin et al 1956) Other French workers have also stressed the value of prednisone in treating the œdematous syndrome of cirrhosis (Cattan and Vesin 1955, 1956, 1957, Fraisse et al 1957a and b), and it is remarkable that this effect was not observed in the Singapore series On the contrary, using similar dosages of prednisolone to those of prednisone used by the French workers, there appeared to be even more ascites and œdema than in the control cases

The most consistent effect of prednisolone in the Singapore series was an improvement in the serum-proteins, with the albumin rising and gamma-globulin falling towards normal levels Although only 1 of the 27 patients in the prednisolone series developed a peptic ulcer—one of the recognised complications of prednisolone therapy (Wells 1957)—other complications of the treatment in cirrhosis have been met, including glucosuria (Dupuy et al 1957), fatal peritonitis, fatal hypokalæmia, reactivation of pulmonary tuberculosis (Fraisse et al 1957a and b), and spinal collapse due to severe osteoporosis (Wells, unpublished) With careful management, however, most of the complications of prednisolone therapy can be prevented or minimised, and the results of the Singapore trial indicate that the administration of prednisolone and corticotrophin reduces *mortality and morbidity*, and improves liver-function tests in severe hepatic cirrhosis

Summary

A controlled therapeutic trial in severe hepatic cirrhosis is described During the trial, 27 control cases had a 55% mortality compared with a 26% mortality in 27 cases treated with prednisolone and corticotrophin, and a 31% mortality in 27 cases treated with testosterone propionate The morbidity of the surviving patients also appeared to be reduced, and the liver-function tests to be improved, by both corticoid and testosterone therapy

The clinical effects of the two treatments showed some differences, suggesting that combined treatment with prednisolone and testosterone might be more effective in cirrhosis than either treatment given alone

I am grateful to Prof G A Ransome for permission to carry out this trial, and to the medical and non-medical staff of Medical Unit I at the General Hospital, Singapore, for their cooperation

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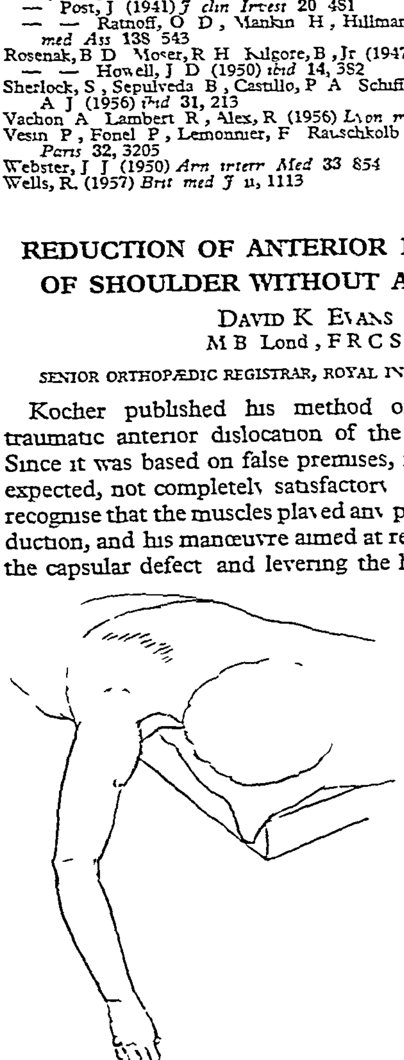
REDUCTION OF ANTERIOR DISLOCATION OF SHOULDER WITHOUT ANÆSTHESIA

DAVID K EVANS
M B Lond, F R C S

SENIOR ORTHOPÆDIC REGISTRAR, ROYAL INFIRMARY, SHEFFIELD

Kocher published his method of reducing recent traumatic anterior dislocation of the shoulder in 1870 Since it was based on false premises, it was, as might be expected, not completely satisfactory Kocher would not recognise that the muscles played any part in hindering reduction, and his manœuvre aimed at relaxing and opening the capsular defect and levering the humeral head back through it into the glenoid cavity Nash (1934), reporting 46 "new" methods published during the next fifty years, deduced that Kocher's method had not been consistently successful in reducing shoulder dislocations without anæsthesia A further argument against it was that the humeral neck or shaft was some-



A modification of Kocher's method, using general anæsthesia, recumbency, and traction—taught in most accident departments in this country—proves successful in nearly every case Since reduction is easily performed by simple traction when the patient is fully anæsthetised and relaxed, this modified Kocher's method is unnecessarily complex Muscular and not capsular relaxation is the key to reduction, and if the stretched (and therefore painful) muscles are relaxed by putting the patient in a suitable position, reduction by traction *without* anæsthesia can be just as easy

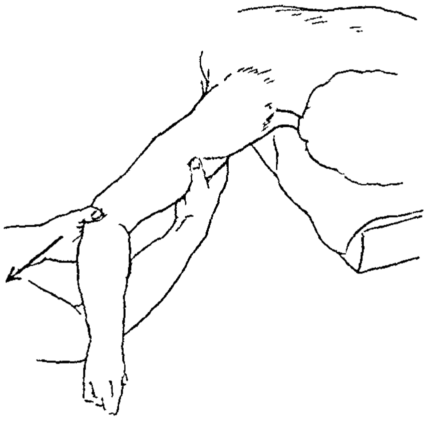


Fig 2—Traction with elbow flexed and shoulder abducted

No originality is claimed for the method used at the Sheffield Royal Infirmary It is substantially that described by Lacey and Crawford (1952) as a modification of Milch's method (1938, 1949) It is simple, painless, and effective

Hanging-arm Technique

The patient lies face downwards on a couch, with a pillow beneath the head and chest The arm on the affected side is allowed to hang freely over the side of the couch, the dislocated shoulder projecting well over the edge so that there is no pressure on the humeral head (fig 1) This position eases pain, and reduction occasionally occurs spontaneously when it is assumed The procedure is explained simply to the patient, he is reassured that it is not painful, and the necessity for complete relaxation on his part is impressed on him

The surgeon then sits on a low box, and grasps the humeral epicondyles His other hand is placed on the inside of the upper arm The patient's forearm is flexed and lies across the bend of the surgeon's elbow (fig 2) Slow steady traction is then kept up, the arm being gently abducted, flexed forward, and slightly internally rotated Reduction often occurs imperceptibly In other cases, the hand in the axilla is used to lift the humeral head gently back into the glenoid cavity (fig 3)

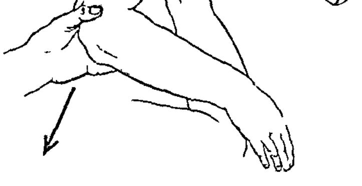


Fig 3—Humeral head is lifted into glenoid cavity, traction being maintained

Surprisingly, the easiest reductions have been in well-built muscular young men, and, when difficulties have been met, they were usually in the frail elderly patient who found the prone position difficult to tolerate In these patients, an injection of 50 mg of pethidine twenty minutes beforehand has eased reduction

This technique has been tried on 50 anterior dislocations of the shoulder, and reduction has been easily and painlessly achieved in 43 Most of these reductions have been made by newly qualified house-officers, who invariably become more proficient with practice These figures could easily be bettered by those well versed in the method

I consider that Kocher's method should be abandoned in favour of this easy procedure which avoids general anæsthesia

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BROMELAIN AND THE CERVIX UTERI

SHEILA L B DUNCAN
M B Glasg , M R C O G
REGISTRAR,
VICTORIA INFIRMARY, GLASGOW, AND FALKIRK ROYAL INFIRMARY

JAMES H LAWRIE
M D Edin , F R C S E , D P H
LATE DEMONSTRATOR,
DEPARTMENT OF ANATOMY, UNIVERSITY OF GLASGOW

HECTOR R MACLENNAN
M D Glasg , F R C O G , F R F P S
SENIOR CONSULTANT GYNÆCOLOGIST, VICTORIA INFIRMARY, GLASGOW

BROMELAIN has been used in the treatment of dysmenorrhœa by Hunter (1957) and Simmons (1958) Both reported relief in most of the cases that they treated

Bromelain is a mixture of enzymes prepared from the stems of pineapple plants Hunter (1957) thought that the preparation had a proteolytic property, and Simmons (1958) refers to a spasmolytic effect Hunter (1955) said also that it was mucolytic, and used it to clear cervical mucus in infertility

To test the preparation for toxicity, Simmons (1958) injected it subcutaneously in mice, and produced an area of necrosis Intraperitoneal injection caused gelatinous peritonitis When he applied it locally to the vagina and to the portio vaginalis of the cervix, it appeared to cause softening only

Further study of its effect on the human cervix seemed desirable before its repeated use became widespread in young women with dysmenorrhœa or infertility, as the possibility of damage to the cervix, the external os, and the cervical mucosa of the internal os might contraindicate its extended clinical use

The effects of similar enzymes, notably papain, have been studied in other fields

The proteolytic effect of papain has been used to " tenderise " meat When the enzyme is used in a gastric lavage during the investigation of gastric tumours by exfoliative cytology, there is a greater yield of tumour cells without alteration of structure (Boyd 1956) Electronmicrographs of collagen, after treatment with papain, show loss of structure of varying degree in the collagen fibres—appearances similar to those found after the action of heat or alkali (Lelli and Arangio-Ruiz 1956) Crude papain administered intravenously to young rabbits brings about ear collapse within twenty-four hours from a specific effect on cartilage (Craigmyle 1959) Kurzrock (1948) stated that papain liquefied cervical mucus

The proteolytic enzyme, trypsin, is used to spread cells grown in tissue culture, without damage to them or alteration to their rate of growth or division Chymotrypsin has been found to depress greatly or to abolish the spontaneous contractions of rabbit intestine in vitro The spasmodic response of the intestine preparation to acetylcholine was lost (Lu 1952)

When bromelain was used by Hunter et al (1957) to clear cervical mucus during hysterosalpingography, cervical dilatation took place Some cases showed a definite effect, and were held to have "physiologically incompetent internal os" The evidence of mucolysis was not altogether convincing as it was based on the enzyme's effect in hydrolysing hyaluronic acid, an important constituent of mucus Hyaluronidase itself, however, does not liquefy cervical mucus (Kurzrock 1948)

Later work by Hunter and his co-workers showed that cervical dilatation with bromelain was associated with contraction of the uterine cornua A similar effect was produced by the enzymes of semen (Hunter 1960) In view of these various findings, this investigation was planned to assess the proteolytic, mucolytic, and spasmolytic effect of bromelain upon the human cervix uteri

The material used was takamine bromelain prepared from Hawaiian bromelain It was prepared by dissolving 75 mg of the extract in 50 ml of a phosphate buffer at pH 5 5 The solution was then Seitz-filtered and freeze-dried after the manner described by Simmons (1958)

Proteolytic Effect

Method—Six women were chosen in whom the cervix appeared to be clinically normal but who required hysterectomy for functional uterine bleeding

The prepared bromelain was dissolved in 50 ml of sterile water and instilled into the vagina at periods of time varying from 20 minutes to 12 hours before removal of the uterus

In five cases the uterus was removed by abdominal hysterectomy and fixed in formalin The specimen was given to one of us (J L), but no information was provided about the exposure of the cervix to bromelain In the sixth case the uterus was removed by vaginal hysterectomy, the operation being carried out in two stages Half the cervix was removed untreated and used as a control Bromelain was applied to the vagina and to the remainder of the cervix After 20 minutes' exposure, the operation was completed by removal of the uterus and the remaining half of the cervix

A further specimen was treated in vitro only A normal cervix, removed at hysterectomy, was divided into four parts One part was fixed as a control, and the others were exposed to bromelain for 12, 24, and 48 hours respectively before fixation

All specimens of cervix were fixed in formol-corrosive, and sections 10 μ thick were stained by four methods—hæmatoxylin and eosin, toluidine-blue, Verhoeff's stain, and van Gieson—to demonstrate (1) any change in the epithelium of the vagina or cervical canal, (2) any alteration in the contents of the cervical glands or cysts, or (3) any abnormality in the smooth muscle, collagen fibres, or elastic fibres Comparison was made with cervices removed untreated

Results—In vivo, no histological changes of any kind were noted in any of the sections examined, regardless of the period of treatment by bromelain

In the specimens treated in vitro for 12 and 24 hours, no histological change was observed The 48-hour specimen showed loss of cell-membrane outline and discrete fibre formation, only the nuclei being visualised within normal limits

Mucolytic Effect

Method—A number of specimens of mucus were obtained both from the cervical canal and from distended intracervical glands A small amount was placed in a watchglass and covered with bromelain in solution The bromelain was left in contact for varying times, and a control specimen covered with saline was used Direct observations, by frequent tilting of the watchglass, were made

Result—There was no immediate effect "Free" cervical mucus was apparently unaffected by exposure to bromelain for 24 hours, but was liquefied after 48 hours

The more tenacious mucus from nabothian follicles required exposure for 3 to 4 days before it was liquefied

Physiological Effect

Method—Three further specimens of the uterus and cervix were obtained immediately after hysterectomy The uterine muscle and tissue of the cervix appeared to be anatomically normal, and it was assumed, since the patients were premenopausal, that they were still responding to the presence of sex hormones

The specimens were placed immediately in ice-cold Krebs' physiological saline Small strips, 1 cm long and 1 cm thick, were cut from the body and the cervix, circularly and longitudinally, and these were suspended in a bath of saline at 37°C, aerated with 95% oxygen and 5% carbon dioxide One end of the strip was attached to the stylus of a kymograph

Results—In agreement with all observations on the movement of human uterine muscle, the contractions were variable Contractions from the body were of larger amplitude than those from the cervix The usual pattern was a composite one of several waves, each of different amplitude, superimposed on one another The response to oxytocin ('Pitocin') was usually an increase in tone with maintenance of the wave pattern at a higher level A striking feature of all the tissues assayed was their endurance, and their ability to maintain an unaltered pattern over a period of up to 12 hours Recognising the wide variations in the normal, it was obvious that observations on the addition of any drug must be interpreted with caution

When bromelain was added, no immediate effect was observed either on spontaneously contracting tissue or on oxytocin-induced contractions In six of seven tissues examined, a slow inhibition of contractions was observed, starting after 20 minutes and causing the contractions to fade in a few hours In view of the normal persistence of contractions this appeared to be significant Washing out the bromelain by two changes of solution did not reverse this slow inhibition

In one specimen of very vigorous uterine-body muscle, no inhibition was observed This particular specimen had not shown any response to oxytocin, but this was not unique as several other specimens had shown little or no response This probably reflects the known variation in response of the intact uterus to oxytocin, depending on the stage of pregnancy, and, to a lesser extent, on the phase of the menstrual cycle

A further experiment was carried out using a rat uterine horn The preparation contracted rhythmically, responded by a spasmodic contraction to the addition of oxytocin, and was inhibited by the addition of bromelain

These observations parallel the experiments on a similar preparation of intestinal smooth muscle, in which the spontaneous contractions are slowly inhibited by the addition of the proteolytic enzyme chymotrypsin, and in which the spasm induced by acetylcholine is also inhibited (Lu 1952)

It appears therefore, that, in vitro, preparations of human uterine and cervical muscle, contracting spontaneously or in response to oxytocin, are slowly inhibited in most cases by the addition of bromelain

Discussion

Proteolytic Effect

If the proteolytic effect of the enzymes of bromelain were held to be damaging or harmful, a penetration of the intact epithelium of the vaginal vault or cervical canal would be expected to result in some damage to the tissue, either by desquamation of epithelium or by an increase in mast-cells in the deeper tissues Within the limits of the staining methods used, no damage was seen

Changes in intact tissues have been found by other workers both in animals and in tumour cells from the human stomach In the former case, the dose may have been greatly in excess of that used clinically for dysmenorrhœa, and, in the latter, tumour cells are known to be less cohesive than normal epithelium and would therefore separate more readily

Where bromelain is used, as advocated by Simmons (1958), the proteolytic effect has not been demonstrated It should be remembered, however, that histological damage was evident when the preparation had been in contact with the cervix for 48 hours in vitro Consequently, care should be exercised in the application of the substance locally so that it is not retained in the vagina for an unlimited period of time

Mucolytic Effect

Prolonged close contact was required to liquefy cervical mucus It may be that the clearing effect of cervical mucus found by Hunter (1955) was due more to the mechanical effect of injecting a solution intracervically than to a specific enzymatic effect

The immediate relief of dysmenorrhœic pain, described by Simmons (1958), cannot be attributed to a mucolytic effect

Spasmolytic Effect

The observations on the effect of bromelain on rhythmically contracting cervical muscle suggest that the enzyme inhibits spontaneous contractions The inhibition is of relatively slow onset, and is greater when the muscle is in spasmodic contraction due to oxytocin This latter effect may be caused by interaction with oxytocin which is itself a polypeptide

The basic cause of the pain of dysmenorrhœa is unknown, but " spasm " has often been suggested It may be that an abnormal state of cervical spasm is inhibited by bromelain

Conclusions

Applied topically, bromelain produces no histological change in the normal intact human cervix Its mucolytic action is slow

Oxytocin-induced spasm of cervical muscle is reduced by bromelain

The mechanism of its alleged action in dysmenorrhœa is uncertain, but our observations suggest that its action may be antispasmodic

Within the limits of this investigation, no harmful effect was found In the light of our present knowledge it would be difficult to support the claim that dysmenorrhœa is relieved in later cycles after a single application

Summary

The action of bromelain on the human cervix has been investigated Claims made for its immediate proteolytic and mucolytic effect have not been substantiated A spasmolytic effect is suggested Its use does not appear to be harmful, and wider trial in dysmenorrhœa is suggested

We should like to thank Prof G M Wyburn and Dr Paul Bacsich of the department of anatomy of the University of Glasgow, and Prof R C Garry of the department of physiology, for the helpful advice and technical assistance which they afforded us We should also like to record our thanks to British Schering who supplied the bromelain, and to Dr A M Goodspeed for information about it

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PSEUDOACANTHOSIS NIGRICANS

SHELAGH M TIGHE
M B Sheff, M R C P, D C H
REGISTRAR, RUPERT HALLAM DEPARTMENT OF DERMATOLOGY,
SHEFFIELD ROYAL INFIRMARY

THE clinical and histological changes in the skin are similar in pseudoacanthosis nigricans and acanthosis nigricans The two conditions must be distinguished, for acanthosis nigricans, occurring for the first time in adult life, is associated with underlying malignancy changes in all cases (Curth 1952), whereas pseudoacanthosis has no dire significance

Six cases of pseudoacanthosis nigricans are reported here to draw attention to the changes that take place in the skin, often in healthy adults These changes can be distinguished from the much rarer and more serious condition of " malignant " acanthosis nigricans

Juvenile acanthosis nigricans is not considered because of the ease with which it is distinguished from the other two conditions

Incidence

Six patients with pseudoacanthosis nigricans attended the Rupert Hallam Department of Dermatology during the

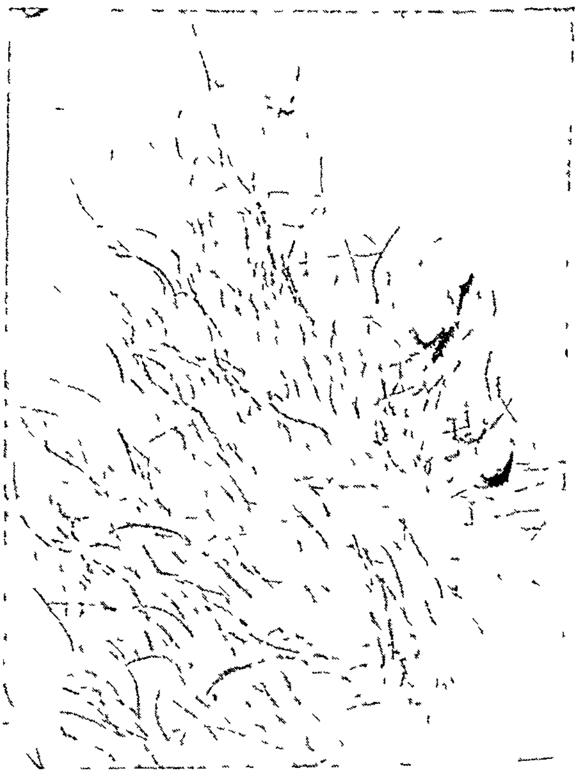

Fig 1—Pseudoacanthosis nigricans in axilla

CASES OF PSEUDOACANTHOSIS NIGRICANS

Case no.	Sex	Age (yr)	Weight (lb)	Height (in.)	Complexion	Distribution of skin lesions
1	M	31	29[illegible]		Dark	Axillæ groins, natal cleft
2	M	47	203	66	„	Axillæ, groins natal cleft, sides of neck
3	F	43	201	67	„	Axillæ, groins natal cleft
4	M	31	23[illegible]	70	„	Axillæ, groins, natal cleft
5	M	3[illegible]	20[illegible]	68	„	Axillæ, groins natal cleft, sides of neck
6	M	67	250	69	„	Axillæ, groins natal cleft, buttocks

last eighteen months The total number of new patients attending in this period was 7863 One patient with "malignant" acanthosis nigricans was seen during this time.

Clinical and Histological Findings

The six patients with pseudoacanthosis nigricans were all obese, and the development of skin changes coincided with their weight gain They were in good general health, and had sought advice for removal of the skin tags The skin changes were mainly confined to the axillæ (fig 1), natal cleft (fig 2), and groins, in these areas the skin had a thickened velvety appearance with dark-brown pigmentation and numerous papillomatous skin tags No underlying malignant disease was found in any of the patients

The accompanying table summarises the main features of these cases

Case 6 was particularly interesting This patient's skin changes had been present for over ten years Eight years ago carcinoma of the penis was successfully treated by radiotherapy Careful follow-up examinations have revealed no local recurrence or metastatic deposits The skin changes did not alter either with the development or with the treatment of the carcinoma.

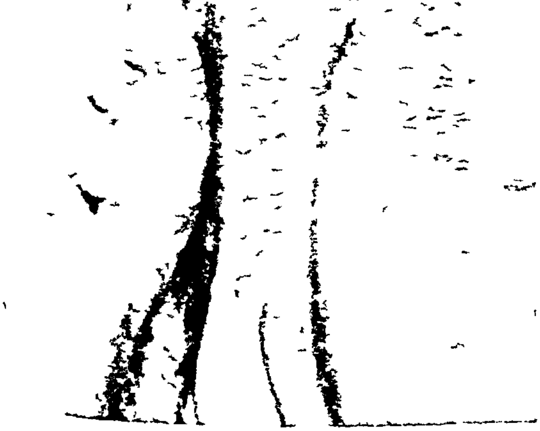

Fig 2—Pseudoacanthosis nigricans in natal cleft.

In the group as a whole the histological skin changes were much milder than those of acanthosis nigricans, and consisted of a filiform papillomatosis, slight epidermal acanthosis, and basal-cell hyperpigmentation

Discussion

Becker (1929) suggested that mild changes of acanthosis nigricans would be found more often in obese patients Curth (1951) gave the name pseudoacanthosis to a condition simulating acanthosis nigricans, which occurred in the body creases of obese brunettes She observed that the changes in pseudoacanthosis nigricans appeared with gain of weight and disappeared with loss of weight. Clinically and histologically, all changes were much milder than in acanthosis nigricans Casals (1950) had already described the condition (Curth 1953)

Patients with carcinoma do not usually gain weight owing to increasing deposition of body fat, whereas all six patients with pseudoacanthosis nigricans had increasing obesity

The skin changes in pseudoacanthosis are much milder, and more limited to body creases, than in acanthosis nigricans The changes in acanthosis are more florid, and often affect the flexor surfaces of the elbows and knees, the backs of the hands, face, breasts, abdomen, forearms, and lips as well as the body creases Confined skin lesions suggest the harmless disorder

Although case 6 had carcinoma, his skin changes were never extensive. The tumour was not the highly malignant adenocarcinoma with which all cases of "malignant" acanthosis nigricans have been associated (Curth 1953) The skin lesions did not regress with successful treatment of the tumour, but the patient has remained in good health for eight years From this I assume that his skin changes and neoplasm are not associated

Curth (1953) suggested that the endocrine factors causing obesity may play a part in producing the skin changes in pseudoacanthosis nigricans, and that these factors may also be important in the pathogenesis of true acanthosis nigricans The skin changes in pseudoacanthosis nigricans, however, are more likely to result from the increased friction and hyperhidrosis of pendulous body folds in fat people In dark-complexioned people the skin readily becomes pigmented with continued friction, as is seen in everyday practice when rubbing shoulder-straps, collar-studs, and belts have, in brunettes, produced brown patches of skin. This would explain the limitation of skin changes in pseudoacanthosis nigricans—a condition probably unrelated to malignant acanthosis nigricans

Summary

Six patients with pseudoacanthosis nigricans have been seen in eighteen months

Pseudoacanthosis nigricans should be distinguished from the "malignant" type of acanthosis nigricans Increasing obesity, coinciding with the development of mild skin changes confined mainly to the body creases, suggests the benign condition of pseudoacanthosis nigricans

I wish to thank Dr I B Sneddon for permission to publish these cases, and for his helpful advice

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POSSIBLE TERATOGENIC EFFECT OF TOLBUTAMIDE IN A PREGNANT PREDIABETIC

YNGVE LARSSON
M D Stockholm
ASSISTANT PROFESSOR OF PÆDIATRICS

GORAN STERKY
M D Stockholm
SENIOR RESIDENT

From the Pædiatric Department of Karolinska Institutet, Crown Princess Lovisa's Children's Hospital, Stockholm, Sweden

THERE seems to be general agreement that the oral sulphonylureas have no effect in juvenile diabetes (Bertram et al 1957, *Lancet*, 1959, Forsham et al 1959, Goldner et al 1959, Oberdisse 1959, Williams 1960) The hypothesis has been put forward, however, that some remaining β-cells in early juvenile cases may be stimulated by the sulpha drugs to produce more endogenous insulin Early combined insulin-tolbutamide therapy intensifies the postinitial stabilisation phase (Larsson, 1958, 1959a and b) Similar results have been reported by others (Bloch 1959, Engleson 1959, Otto and Mai 1959)

The use of oral sulphonylureas in the prediabetic state to prevent decompensation of the islet tissue was suggested by Jackson (1959) and investigated by Fajans and Conn (1960), who found that tolbutamide improved the carbohydrate tolerance in thirteen out of fourteen young non-obese symptomless diabetics

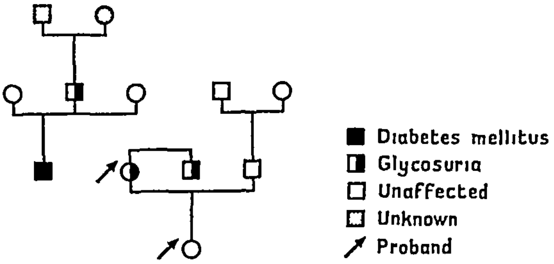

Fig 1—Family tree

The use of tolbutamide in prediabetic pregnancies—by analogy with the insulin treatment introduced by Wilkerson (1959)—would be the next logical step As far as we know, however, no such trials have been made, though Mestwerdt (1959) says that sulphonylureas are valueless in the treatment of diabetic pregnancies Burt (1958), who studied the effect of tolbutamide in normal pregnancy, mentions that he found resistance to the hypoglycæmic effect of tolbutamide resembling that found with insulin

A teratogenic action of carbutamide has been described by de Meyer and Isaac-Mathy (1958) and by Tuchmann-Duplessis and Marcier-Parot (1959) in the offspring of pregnant rats Most of the congenital defects were confined to the ophthalmic region

We describe a young woman with symptomless diabetes whose carbohydrate tolerance was greatly improved by tolbutamide While under continuous treatment with tolbutamide, she became pregnant and gave birth to a child with multiple congenital malformations

Case-report

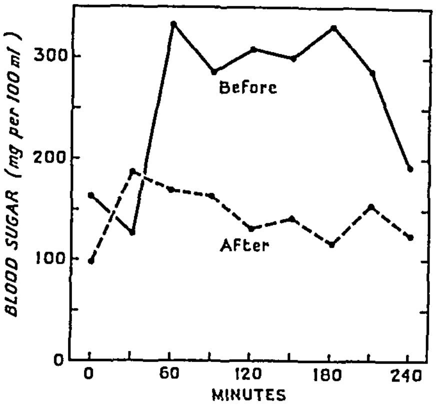

Fig 2—Glucose-tolerance tests, before and two weeks after tolbutamide treatment

A 14-year-old girl was sent to us in December, 1957 by her school doctor, who had found sugar in her urine She had no diabetic symptoms, but there was a family history of diabetes A half-brother—her father had married twice—had been a severe juvenile diabetic for many years Another half-brother and her father had had asymptomatic glycosuria several times The family tree is shown in fig 1

The patient was well nourished, though not obese bodyweight 53 8 kg (118 lb), height 158 cm (5 ft 2 in) She had moderate glycosuria, with a daily excretion of 2–5 g of glucose No acetonuria Her fasting blood-sugar levels were normal, but a double oral glucose-tolerance test (G T T) yielded a "diabetic" response with a maximal blood-sugar value of 330 mg per 100 ml The same day her twenty-four-hour urinary output of glucose increased to 15 7g Asymptomatic diabetes was diagnosed Before insulin therapy was started, a trial was made of tolbutamide After two weeks' daily administration of 2 g of tolbutamide, another double oral G T T was made The patient's carbohydrate tolerance was now completely normal (fig 2) Because of this satisfactory response to oral treatment, we decided that there was no indication for insulin therapy Continuous tolbutamide treatment was prescribed Moderate dietary restrictions—which the patient followed only sporadically—were prescribed, and she was regularly seen at our diabetic clinic The dose of tolbutamide was lowered stepwise, and after three months, she was taking 0 5 g daily

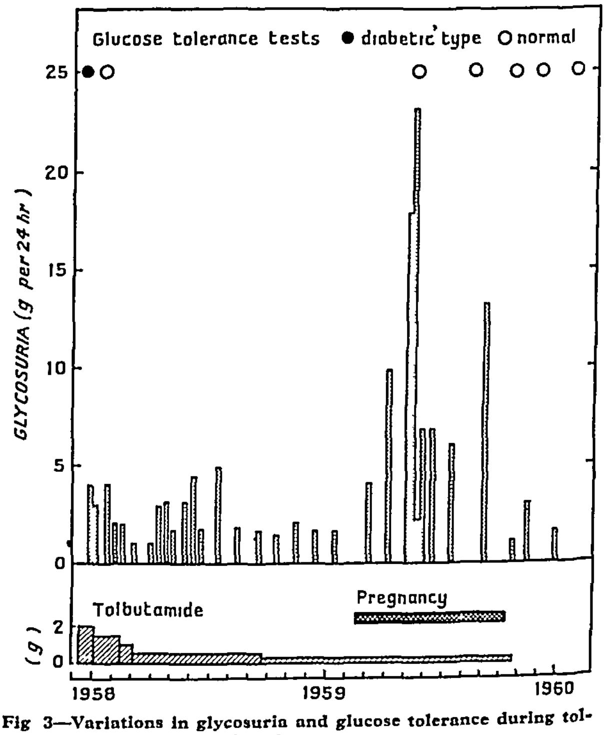

Fig 3—Variations in glycosuria and glucose tolerance during tolbutamide treatment and during pregnancy

The patient continued to have normal fasting blood-sugar levels, but still excreted a few grammes of glucose every day (fig 3)

In April, 1959—i e, after a year and four months of tolbutamide treatment—glycosuria increased, and the patient, now 16 years of age, was found to be pregnant Her general condition was good, and she weighed 54 7 kg (120 lb). The fasting blood-sugar was normal, and repeated G T T s were also within normal limits Blood-cholesterol, total lipids, creatinine were all normal, as also were electrophoretic studies She belonged to blood-group O, Rh-positive A renal-function study showed normal clearance values—*p*-aminohippuric acid 1343, endogenous creatinine 190, and inulin 270 ml per 1 73 sq m body surface Twenty-four-hour excretion of 17-ketosteroids 4 3 mg, and of corticosteroids 5 6 mg

Interruption of pregnancy was considered, but, as the diabetic state was under complete control and the patient was anxious to have her baby, this was not undertaken Tolbutamide was continued. Six weeks before full term, labour started spontaneously After seven hours, the patient gave birth to a premature female infant, weighing 1100 g (2 4 lb), who died fifteen minutes later The placenta contained two small infarcts, but was otherwise normal

The puerperium was uneventful After delivery, the tolbutamide treatment was stopped Fasting blood-sugars and G T T have remained normal The response to an intravenous-tolbutamide-test, by the method of Unger and Madison (1958) was also normal

Necropsy on Infant

The hands and feet were malformed, each hand had only four fingers, with syndactyly between the second and third fingers, and between the toes The external ear was malformed, and the external auditory canals were atretic The eyes and optic nerves were normal There was internal hydrocephalus The left part of the diaphragm was absent, and parts of the stomach, transverse colon, spleen, and pancreas were found in the thoracic cavity There was dextrocardia, complete absence of the atrial septum, and a small ventricular septal defect The right uterine adnexa were absent The adrenals were large and hyperæmic with a few cortical hæmorrhages

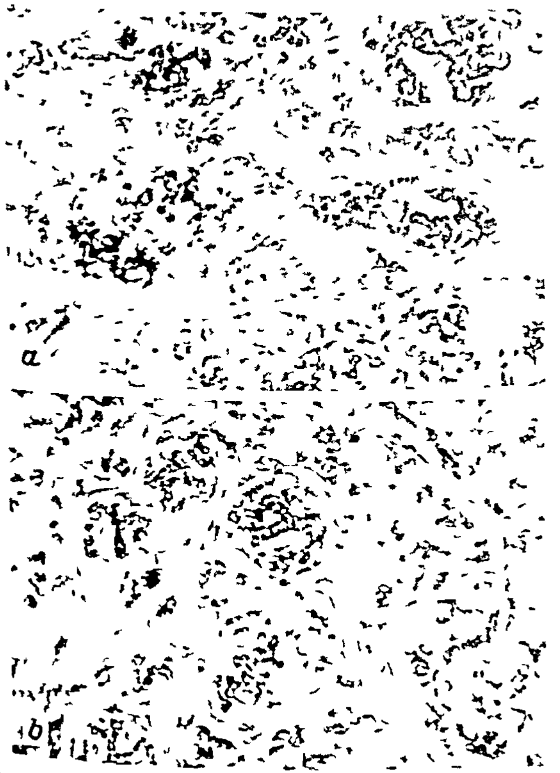

Fig 4—Microscopic appearance of pancreas (×140) *a* in infant of present case *b* in premature child who died from acute meningitis one week after birth.

The pancreas was macroscopically normal Microscopically, the acini were also normal The islet tissue showed no signs of hyperplasia when compared with the pancreas from an infant of the same gestational age and size (fig 4) If anything, the islets were smaller and sparser than normal A differential count of 1500 islet-cells showed 44% β-cells and 56% α-cells These figures are roughly the same as those found in comparable control material

Discussion

No satisfactory explanation can be found for the congenital defects in this infant The incidence of congenital malformations is greater than normal in diabetic and prediabetic pregnancies (Hagbard 1956, Hoet and Boerman 1951, Oberdisse 1959, Crampton 1960) All types of congenital defects have been described Another typical finding is hyperplasia of the pancreatic islets, which sometimes may be the only sign suggesting maternal prediabetes (van Beek 1952) Jackson (1959) found the islet-pancreas relation to be 6 5% in still-births of diabetic mothers and 7 5% in those of prediabetic mothers, while in control material, the value was 1 3%

The absence of islet hyperplasia may indicate that the disturbance of carbohydrate metabolism in the mother was not the cause of the defects in the infant On the other hand, the adrenal hyperplasia observed at necropsy is consistent with the observations of Hoet and Boerman (1951) and Hoet (1954a and b), suggesting that cortical hyperfunction may be a contributory cause of diabetic embryopathy

The possibility that tolbutamide given to the mother may have caused the defects of the infant cannot be excluded Experimental observations (de Meyer and Isaac-Mathy 1958, Tuchmann-Duplessis and Mercier-Parot 1959) support this hypothesis The mechanism of this teratogenic effect is unknown Two factors—hypoglycæmia and hypothyroidism—both of which may be produced by tolbutamide treatment, have experimentally caused congenital malformations (Brown and Solomon 1956, Lichtenstein et al 1951, McGavack et al 1957) Although there were no clinical signs of low blood-sugar or lowered basal metabolism in our pregnant patient, these effects of the drug may have been active in the fœtus

As the possibility of a tolbutamide-induced lesion cannot be excluded, we think it wise not to use the sulphonylureas during pregnancy In prediabetic pregnancies, insulin and a proper diet may be safer (Wilkerson 1959)

Summary

In a young woman with symptomless diabetes mellitus, the carbohydrate tolerance was kept normal with tolbutamide She became pregnant during the time she was receiving tolbutamide, and gave birth to a child with multiple congenital deformities These defects may possibly have been caused by the sulphonylurea therapy

We thank Prof G T Hultquist, Uppsala, for the histological investigation of the pancreas, and Dr A Bergstrand, Sabbatsberg s Hospital, Stockholm, for the rest of the pathological examinations

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COLLECTION, STORAGE, AND ADMINISTRATION OF AUTOLOGOUS HUMAN BONE-MARROW

D E PIGG
M B Lond
LECTURER, DEPARTMENTS OF HÆMATOLOGY AND RADIOTHERAPY,
WESTMINSTER HOSPITAL, LONDON, S W 1

N H KEMP
M B Lond
REGISTRAR, DEPARTMENT OF HÆMATOLOGY,
ST GEORGE'S HOSPITAL, LONDON, S W 1

THE treatment of disseminated malignant disease with high-dosage chemotherapy or wide-field irradiation has been described in several reports (Kurnick et al 1958, Bagshawe and McDonald 1960, Jack et al 1960) Many workers have used autologous bone-marrow therapy to try to overcome the severe hæmopoietic depression which follows use of these methods (Kurnick 1959, McFarland et al 1959, McGovern et al 1959, Newton et al 1959, Westbury et al 1959, Jones et al 1960) The alternative of homologous bone-marrow transplantation has generally produced unsatisfactory results (Thomas et al 1959, Mathé et al 1959, 1960) either the marrow has failed to "take", or, when it has, secondary disease has often ensued As a planned procedure, this approach is therefore uncertain and potentially dangerous, although it may be of value in an emergency (Mathé et al 1959, Bielby et al 1960)

Because of the present interest in autologous bone-marrow therapy, a complete description of the technique developed over the past three years may be of general interest The procedure is not regarded as final, but is simple, efficient, and safe for clinical use Techniques of bone-marrow storage are included since they enable protracted therapy to be carried out The method of preservation at −79°C in glycerol fulfils the present requirements for successful storage (Barnes et al 1955, Porter and Murray 1958, Lochte et al 1959)

The following is a list of the apparatus and materials required, together with manufacturers

APPARATUS AND MATERIALS

—	Number	Apparatus, &c	Manufacturer
Contents of single sterile drum	3	Waterfield needles for multiple marrow aspiration, sternal 1 in	Messrs Chas Thackray, London, W 1
	3	" " " " " iliac 2 in	" " " " "
	2	3 way taps " " " "	" " " " "
	2	Needles for direct attachment of tubing, 10 in	" " " " "
	1	Needle " " " " " 6 in	" " " " "
	3	Needles " " " " " 2 in	" " " " "
	2	Needles, Luer, 1 in 17G	" " " " "
	10	All glass syringes, 20 ml (Luer Lok)	" " " " "
	1	" syringe 30 ml "	" " " " "
	2	Transverse handle needles	Messrs A L Hawkins, London, W 1
	2	3 ft lengths silicone rubber tubing (4 mm bore, 1 65 mm wall)	Esco (Rubber) Ltd, London, N 16
	1	Sieving device	Metal Machinists Ltd, London, S W 1
	2	560 ml M R C siliconed dry bottle (graduated)	R B Turner, Ltd, London, N 2
Other materials		TC 199	Glaxo Ltd
		Pure freeze dried heparin	Evans (Medical), Ltd
		Analar glycerol	B D H Ltd
		Plastic disposable giving set	Capon Heaton & Co, Ltd
		1 oz Alkathene ampoules *	Messrs Fibrenyle, London W 3
	1	Small soldering iron 25W 'Solon'	Henley Ltd, London, E C 1
	1	Two stage cooling apparatus	Matburn, Ltd, London, W C 1
	1	79 C storage cabinet	Metcold, Loughborough, Leics

* These ampoules should be packed in polyethylene sleeving 150 gauge 2 in wide (Hughes Brushes, Ltd, Slough, Bucks), which is sealed with the Audion Sealboy 700 instrument (F R C Robinsons Paper Co, London E 14)

Dr D B Powell (The Technological Irradiation Group, Grove Airfield, Wantage, Berks) has kindly undertaken to sterilise them by γ irradiation to 2 5 Mrads For this, the ampoules should be packed in boxes, 13 × 9½ × 7¾ in, obtainable from Taylor Gilbert, Ltd, London, E 3

Methods

In the normal human adult, bone-marrow may be obtained by needle-puncture (Wilson 1959, Mathé et al 1959) or by surgical excision from the bones of the thoracic cage, vertebral column, and pelvis In the cancer patient, however, marrow may be absent from some of these sites because of previous radiotherapy, and, in consequence, marrow may have extended into the long bones Surgical excision involves greater danger and discomfort to the patient, and requires the technical ability of a trained surgeon In our view, this approach is of value only when it is desired to obtain marrow from the ribs Simple aspiration of rib-marrow produces very low yields of cells, whereas an entire rib may be expected to provide $1–2 \times 10^9$ nucleated cells Even this figure compares unfavourably with the yield by multiple aspiration from the pelvis and sternum, and is justified only if these other sites are hypoplastic Occasionally marrow from a rib removed at thoracotomy for carcinoma of the lung may be stored, if further treatment is envisaged Preliminary diagnostic marrow-punctures are always performed to exclude malignant infiltration of the proposed aspiration sites

Collection of Bone-marrow by Aspiration

We favour the Waterfield marrow-biopsy needle (Waterfield 1946) It is comfortable to hold, easy to control, and can be more robustly constructed with a longer and stouter needle for multiple bone-marrow punctures For use in very hard iliac bones, a more satisfactory instrument is that shown at C in fig 1 With this needle, greater pressure and torque may be obtained, while the transverse grip on the needle itself assists both in the withdrawal of the instrument and in the expulsion by the stilette of bone fragments In practice, we use a 1-in

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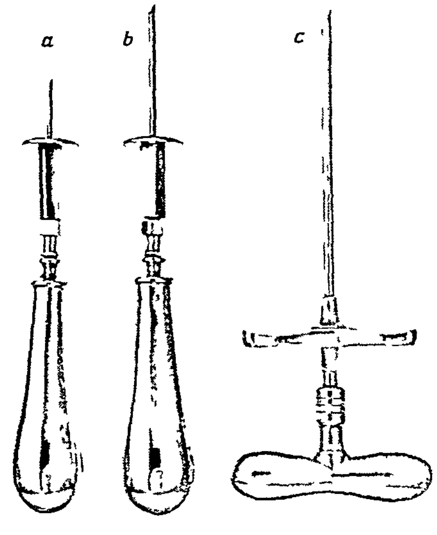

Fig 1—Needles for multiple bone-marrow puncture
Left to right *a*, Waterfield sternal needle, *b*, Waterfield iliac needle, *c*, transverse-handle needle

Waterfield needle for the sternum, and a 2-in Waterfield needle, or the transverse-handle needle, for the ilium All needles have 'Luer-Lok' fittings

In an attempt to obtain absolute sterility of the marrow during aspiration, a closed-circuit system has been employed (fig 2) A 3-way tap is included between the needle and a siliconed 20 ml syringe About 3 ft of silicone-rubber tubing is attached to each side-arm of the tap From one side-arm, the silicone-rubber tubing leads to a dry siliconed sterile bottle (the M R.C 560 ml graduated bottle is particularly convenient) The other side-arm of the tap is connected to a 100 ml vial of tissue-culture medium (TC 199), containing pure freeze-dried heparin at a concentration of 50 units per ml

With the tap in position 1 (fig 2), 4 ml of TC 199 is drawn into the syringe, followed by 16 ml of bone-marrow aspirate with the tap in position 2 Rotation of the tap to position 3 enables the mixed syringe contents to be delivered into the siliconed bottle

Aspiration is done under general anæsthesia with intubation Full sterile precautions are taken in the operating-theatre With the patient supine, multiple punctures are made in the manubriosternum, the anterior superior iliac spines, and anterior iliac crests The posterior iliac spines and crests are then punctured with the patient prone In the pelvic region the skin is sufficiently mobile to enable several bone-marrow punctures to be made through each skin puncture

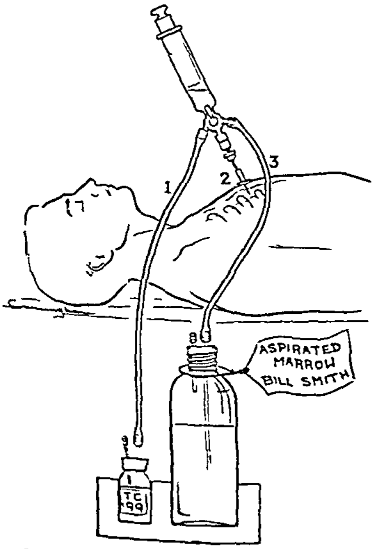

Fig 2—Closed-circuit aspiration system

The needle is advanced, or a fresh puncture made, after each 5 ml of marrow has been aspirated, this ensures minimal dilution with peripheral blood A total of 15–20 punctures is usually made, yielding up to 450 ml of diluted marrow The most fruitful site is the posterior iliac spine, followed by the posterior iliac crest, sternum, anterior iliac spine, and anterior iliac crest, in that order

Collection of Bone-marrow from Excised Ribs

The rib is cut into fragments, each of which is crushed and the pieces placed in a conical flask containing 50 ml of TC 199 with heparin 10 units per ml Gentle agitation of the flask for 30 minutes suspends the marrow cells, and most of the fat, in the culture fluid, which is then transferred to a second bottle (Schwartz and Tocantins 1958)

Manipulation of Marrow in the Operating-theatre

The marrow suspension is sieved in order to break up the fat and marrow fragments before centrifugal separation of the fat The sieving device previously described by Pegg (1960) is used The aspirated marrow is transferred from the bottle to the sieving device by gravity through the silicone-rubber tubing previously attached to the 3-way tap A similar technique is employed for the transfer of rib bone-marrow The marrow suspension is then sieved ten times with the large-mesh plunger (380 μ pore), followed by a similar treatment with the fine-mesh plunger (80 μ pore), the inlet tube being clamped by Spencer Wells forceps After this, the marrow is returned by gravity through the tubing to the original bottle The needles are removed from the bottle, and further processing is carried out in the laboratory

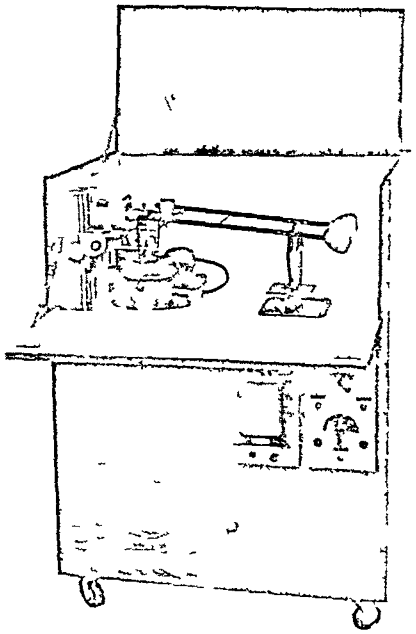

Fig 3—Two-stage cooling apparatus

The aspirated marrow suspension can be delivered directly into the sieving device and then, after sieving, transferred to the bottle, the number of manipulations is thus reduced

Manipulation of Marrow in the Laboratory

Centrifuging is carried out in an ' M S E Major ' or ' Super Magnum ' centrifuge at 1000 r p m for 15 minutes The fat and most of the supernatant are now aspirated through a wide-bore needle attached to a filter pump and trap bottle, leaving a concentrated cell suspension Cell-counts and smears are conveniently made at this stage

Storage at +4°C and Subsequent Administration

Marrow cells remain viable at −4°C for 24 hours, and probably for 48 hours (Billen 1959, Mannick et al 1960) This is long enough for certain purposes, including regional perfusion (Creech et al 1959) and the systemic use of short-acting cytotoxic agents (McFarland et al 1959) For this the concentrated cell suspension is diluted with TC 199 and kept at −4°C The stored marrow is infused intravenously through a standard plastic giving-set, incorporating a filter

Storage at −79 C

For periods of preservation exceeding 48 hours, the glycerol two-stage cooling technique is employed (Polge et al 1949)

This is necessary for more protracted systemic chemotherapy (Westbury et al 1959), fractionated wide-field or whole-body irradiation (Kurnick et al 1958, Kurnick 1959, Newton et al 1959), and the storage of marrow removed during remission in leukæmia (McGovern et al 1959) The apparatus used is an improved version (fig 3) of that described by Pegg and Trotman (1959)

The principal modification is the replacement of the thermostat control circuit by a thermistor-operated mechanism This, in addition to lowering the beaker at −15°C, switches on the fan over the temperature ranges ambient to +10°C and −15°C to −40°C This ensures adequate dispersal of froth without excessive evaporation from the cold sink An additional light indicates when the cooling process is completed Other modifications include the replacement of the wax moulding in the cooling chamber by polytetrafluoroethylene (' Fluon '), which is more durable and has identical thermal properties

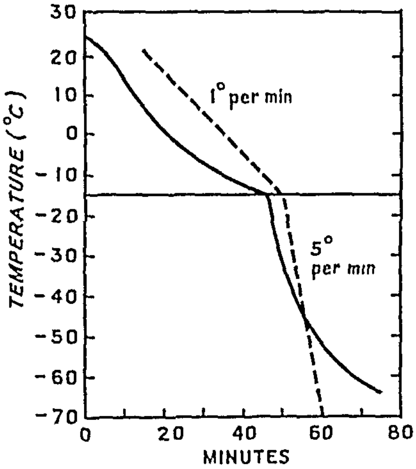

Fig 4—Two-stage cooling curve

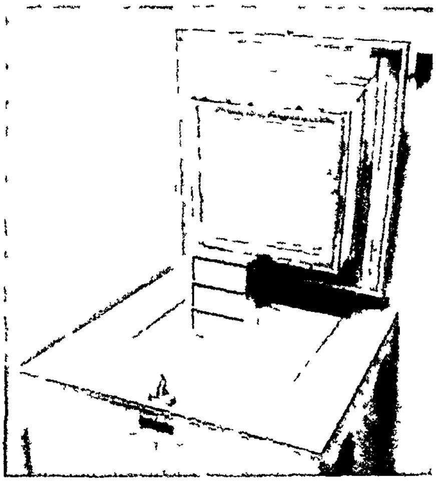

Fig 6—Bone-marrow storage unit

The shape of the ampoule rack has been altered to accommodate eight 1 oz ' Alkathene ' ampoules, and the efficiency of the two stirrers has been increased by using an archimedean screw The apparatus has thus been made completely automatic and will cool 200 ml of marrow-cell suspension The cooling curve is shown in fig 4 Sometimes more than 200 ml of concentrated marrow may be obtained, necessitating two cooling " runs ", the second batch is then held at +4°C before glycerolisation and cooling

To the concentrated marrow-cell suspension, 15% by volume of pure ' Analar ' glycerol is added slowly with constant agitation The viscosity of pure glycerol precludes aspiration into a syringe, and we have found it convenient to remove the plunger of a 30 ml syringe, to pour in the glycerol to the desired volume (30 ml for 170 ml of marrow-cell suspension), and—having replaced the plunger—to inject the glycerol slowly into the bottle through a wide-bore needle Since glycerol is hygroscopic it should be stored in small well-stoppered bottles

A standard plastic disposable recipient-set provides a convenient method of dispensing the glycerol/marrow mixture into the ampoules, at the same time filtering out any fragments of bone, fibrous tissue, or small clots which may be present 25 ml is run into each radiation-sterilised ampoule (Mayernick and Daniels 1959), which is then sealed with a small soldering-iron and a Spencer Wells forceps Glass ampoules have been replaced by polyethylene ampoules because they are less fragile and easier to seal and to open, and the risk of overheating the contents is avoided The ampoules are suitably labelled with permanent ink or pencil

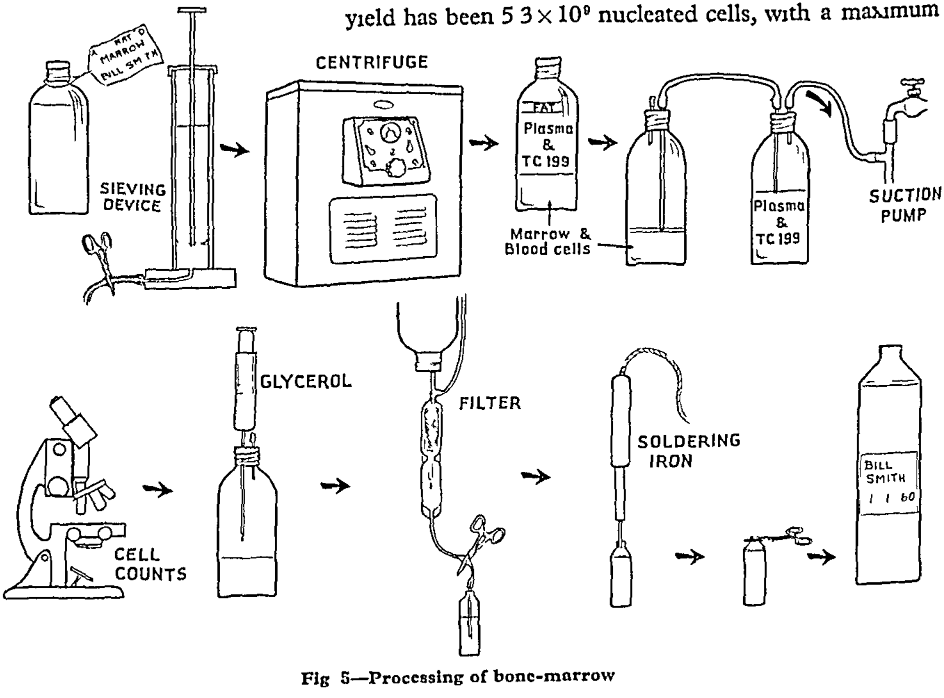

Fig 5—Processing of bone-marrow

The entire process is illustrated in fig 5 After cooling, the ampoules are stored under methylated spirit maintained at −79°C by solid CO_2 We have used a 15-gallon welded aluminium tank enclosed in 8 in of insulation, the ampoules being located in aluminium racks (fig 6)

Administration of Marrow Stored at −79°C

The ampoules are rapidly thawed in a water-bath at 40°C, and the contents immediately injected into an intravenous saline infusion, close to the needle A further ampoule is thawed when the previous ampoule has been successfully injected Each batch is flushed through with saline to reduce the tendency to venous spasm Care is taken to avoid delay between thawing and administration, no attempt being made at deglycerolisation Aliquots are taken for bacteriological culture

Since slow cooling is not ideal for erythrocyte preservation, some hæmolysis of the preserved material is inevitable, and occasionally the recipient has had transient hæmoglobinuria Short-lived pyrexia has also occurred These sequelæ have not led to any further complication and do not appear to affect the success of the infusion

Results

In the last 50 cases of bone-marrow aspiration, the mean yield has been 5 3 $\times 10^9$ nucleated cells, with a maximum of $27 3 \times 10^9$ The series has included 7 children from whom low yields were to be expected We can now expect to obtain $6–12 \times 10^9$ nucleated cells from an adult whose general condition is good and who has not previously received extensive radiotherapy These figures do not allow for dilution with peripheral blood nucleated cells, correction for this would involve a reduction of about 15% in the quoted yields Thus the actual yield of marrow cells is about $5–10 \times 10^9$, or about 0 5 to 1 0% of the total body marrow Animal experiments with whole-body irradiation would lead one to expect that this proportion is of the correct order to afford protection in an autologous system (Alpen and Baum 1958, Lajtha 1960) Results obtained in the treatment of human malignant disease will be described in detail elsewhere

Excised ribs have, in our hands, yielded a mean of $1 1 \times 10^9$ cells per rib in a series of 30 preparations, with a maximum of $2 9 \times 10^9$ cells No correction is needed for peripheral blood-cells

Bacteriological culture of aliquots of the stored marrow have been consistently sterile

Summary

A simple, efficient, and safe procedure for the collection, storage, and administration of human autologous bone-marrow has been developed

Whenever possible, the bone-marrow is obtained by multiple aspiration (15–20 punctures) from the sternum and ilia Excised ribs may be used, though the yield of nucleated cells is comparatively low

To ensure sterility of the marrow, a closed-circuit system of aspiration is used

After sieving, the marrow is centrifuged If it is to be administered within 48 hours, it is diluted with TC 199, and kept at +4°C For periods longer than 48 hours, the marrow is cooled in 15% glycerol by a two-stage technique to −79 C and then stored at this temperature

We are especially grateful to Dr J G Humble, who initiated this project and has provided constant encouragement We gratefully acknowledge the continued interest of Prof R J V Pulvertaft, Prof T Crawford, Dr K A Newton, and Dr J L Stafford The modifications to the freezing apparatus were carried out with the enthusiastic collaboration of Mr R E Trotman Much of the apparatus was constructed under the direction of Mr N H Pierce and Mr A Stewart in the physics workshops of Westminster and St George s Hospitals, with the aid of a generous donation by Mrs S R Newall, and grants from the British Empire Cancer Campaign and the board of governors of Westminster Hospital Our thanks are due to Dr Peter Hansell for the illustrations We should also like to thank Dr D B Powell for γ-ray sterilising facilities, Dr B J Perry for additional technical advice, and Dr A Worlock of Evans (Medical) Ltd for the gift of pure freeze-dried heparin We both acknowledge our gratitude to the British Empire Cancer Campaign for full research grants during the tenure of which much of this work was carried out

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References continued at foot of next column

Preliminary Communication

CLINICAL OBSERVATIONS ON VASOMOTOR REFLEXES IN RELATION TO BLOOD-VOLUME IN OPEN-HEART SURGERY

In open-heart surgery, before disconnecting the heart-lung machine, it is important to replace blood lost from the patient But estimation of the loss may be difficult Direct measurements of body-weight and blood-volume have not been practicable at the time when the information was most needed Examination of towels and swabs from the operating-table may grossly underestimate the amount of blood lost

The arterial pressure during heart and lung bypass may be a misleading guide to hypovolæmia, for it is affected by perfusion-rate as well as by the blood-volume of the patient Thus high arterial pressure may result from excessive perfusion, or from a satisfactory level of perfusion in a patient with arterial constriction caused by hypovolæmia Low arterial pressure may be found with normal blood-volume and inadequate perfusion, or with adequate perfusion and vasodilatation At the end of perfusion it may be difficult to decide the level of blood-pressure which ought to be present if the blood-volume is satisfactory For example, hypertension may arise with closure of a septal defect in a healthy young person, but not with repair of an incompetent valve in a patient who has advanced disease

The tone of the venous system varies, and blood-loss may be severe in the face of unchanged central venous pressure In addition, central venous pressure may rise as a result of heart-failure or heart-block in a patient who lacks blood

These observations made it clear that a speedy and simple test for hypovolæmia would be of value in clinical perfusion, and Valsalva's manœuvre suggested a principle which might be employed Forced expiration against a closed glottis raises the intrathoracic pressure and reduces venous return to the heart Blood-flow into the arterial bed decreases, and the arteries constrict At the end of forced expiration blood returns freely to the heart, and a short-lived rise in arterial pressure results from the injection of an augmented cardiac output into a constricted arterial bed

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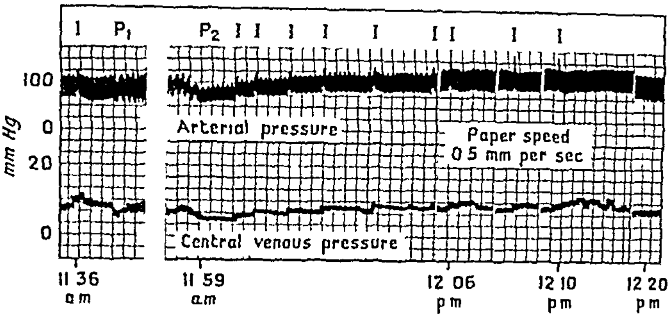
In open-heart surgery, arterial pressure is recorded continuously by means of a catheter in the radial artery, and the effect of squirting blood from the heart-lung machine into the patient's femoral artery immediately before or after perfusion may be observed without difficulty Experience in sixty cases has suggested that squirting blood rapidly into the femoral artery, in quantities of 80–90 ml at a time, has an effect on the arterial pressure which is quantitatively related to the state of the blood-volume In patients with " normal " blood-volume the arterial pressure falls by 5–15 mm Hg for 30-40 seconds This response is invariably found *immediately before perfusion when blood-loss has* been negligible In patients with reduced blood-volume *after perfusion* the arterial pressure rises immediately by as much as 50 mm Hg, and the extent of the rise appears to be proportional to the lack of blood *In patients with " normal " blood-volume* the fall in blood-pressure may be attributed to reflex vasodilatation from sudden distension of the aorta In those with reduced blood-volume the rise in blood-pressure is attributed to injection into a constricted arterial bed



Extracts from the radial arterial and central venous pressure tracing before and after total cardiopulmonary bypass for closure of an atrial septal defect

P_1 and P_2 mark the beginning and end of extracorporeal circulation I marks each squirt of 80–90 ml of blood from the heart-lung machine into the femoral artery

The zero reference point for the pressures lies close to the operating table top The scale therefore does not give absolute values

In clinical practice the injection of 80–90 ml of blood into the femoral artery is repeated until the arterial pressure ceases to rise, or shows a slight fall The heart-lung machine is then disconnected from the patient, and the central venous pressure obtained at this point is maintained by blood-transfusion until the chest is closed

The efficiency of this method of correcting blood-volume at the end of perfusion may be assessed 2–3 hours afterwards when the patient can be examined and weighed Under-correction is revealed by loss of body-weight and by certain signs circumoral pallor, sweating, restlessness, hyperpnœa, peripheral cyanosis, guttering of the superficial veins, hypertension, and venous constriction which slows the flow from a drip bottle Patients showing these signs may die suddenly 8–12 hours after operation Too great a blood-volume may be manifested by venous engorgement, hypertension, pulmonary œdema, and increased body-weight These signs have not been seen in the sixty patients whose blood-volume was corrected at the end of perfusion by the method described

We should like to emphasise that direct measurements of blood-volume have not been made in our patients Blood-volume correction at the end of perfusion has been considered good or bad in the light of clinical examination and weighing 2–3 hours later The reflex fall in pressure obtained when blood-volume is well corrected after perfusion is similar to the reflex fall obtained immediately before perfusion when the blood-loss in preparation for heart and lung bypass has been negligible

CASE-REPORT

A boy of 15 (heart-lung machine case 81) had a surface area of 0 87 sq m, body-weight 34 55 kg, and calculated blood-volume (on the basis of 80 ml per kg) 2 8 litres

With a blood-flow through the patient and extracorporeal circulation of 1 6–1 8 litres per minute, an atrial septal defect was closed during total cardiopulmonary bypass The œsophageal temperature was lowered from 35 to 32°C, and raised to 34 5° during the perfusion which lasted 21 minutes

Arterial and central venous pressure records are shown in the figure At 11 36 A M, immediately before perfusion, the arterial pressure fell reflexly when 80–90 ml of blood was squirted from the heart-lung machine into the femoral artery (I) P_1 and P_2 mark the beginning and end of perfusion As soon as perfusion finished the level of arterial pressure fell from 115/75 to 90/60 mm Hg Nine squirts of 80–90 ml of blood were then given (each marked I in the figure) The first six squirts caused a rise in arterial pressure The seventh and eighth squirts produced no change The last squirt was followed by a small and transient fall in pressure At this point the heart-lung machine was disconnected from the patient Subsequently 880 ml of blood was given by intravenous drip and 406 ml was lost on swabs When the patient was uncovered 2 hours later there were no signs of abnormal blood-volume and weighing on bed scales showed an increase of 600 g over his preoperative weight Recovery was uncomplicated

DISCUSSION

The volume of blood squirted into the femoral artery to diagnose and correct hypovolæmia has been 80–90 ml in patients weighing 30 kg or more This amount was arbitrarily selected as the volume ejected by a single stroke of the pump used for clinical heart and lung bypass[1] A lesser volume was used for small children

A study of vasomotor responses in states of disordered blood-volume is obviously incomplete without direct measurements of blood-volume These have been planned, but their interpretation may not be simple, for indirect evidence suggests that blood may " pool " during long operations The rate of exchange of " circulating " with " pooled " blood, and the rate of release of " pooled " blood may be complicating factors Nevertheless we consider that the clinical observations alone have sufficient value to justify their continued use in simplifying one of the problems of open-heart surgery Moreover the principle of testing blood-volume by the intra-arterial injection of blood may find a place in other branches of clinical practice

SUMMARY

Clinical observations on sixty patients undergoing open-heart operations suggest that vasomotor responses may offer a more reliable guide to blood-volume than the levels of arterial and central venous pressure

The rapid injection of 80–90 ml of blood into the femoral artery may cause the arterial pressure to fall or to rise The fall, which is attributed to reflex vasodilatation, is associated with unimpaired blood-volume The rise

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[1] Nixon, P G F *Lancet*, 1959, i, 1074

appears to be caused by injection into a constricted arterial bed, and the constriction is associated with hypovolæmia

P G F Nixon
M B Durh , M R C P
Research Fellow in Thoracic Surgery

V A Grimshaw
M A , M B Cantab , F F A R C S
Senior Registrar in Anæsthetics

G H Wooler
M A , M D Cantab , F R C S
Thoracic Surgeon

The General Infirmary,
Leeds, 1

Medical Societies

MANCHESTER MEDICAL SOCIETY

Industrial Medicine

At a meeting of the section of general practice on Nov 28, Prof R E Lane spoke on the Doctor in Industry He said that in industry the doctor is concerned with the care of people in their working environment, and his functions are the same as elsewhere—to treat sickness and prevent disease The preventive side is becoming increasingly specialised as industry becomes more complicated, and this frequently involves close cooperation with other experts (e g , the health physicist) The doctor in industry provides a link between the various branches of the National Health Service and industrial management—interpreting general medical requirements to fit specific working conditions The importance of work in the final stage of treatment of many patients cannot be overstressed

The success of the doctor's work in industry depends on his power to secure the cooperation of management and the confidence of workpeople This in turn depends on his integrity and his knowledge of industrial medicine His functions fall into three main groups to see that the workman is fit for his job, to see that the job is fit for the workman, and education Certain medical services in factories are statutory, these are provided by the medical inspector of factories and by some 1600 appointed factory doctors In recent years voluntary industrial health services have expanded Some of the nationalised industries —e g , the National Coal Board and the Atomic Energy Authority—have highly efficient services of this type

The tendency to carry out too many routine medical examinations and do little else is a danger to which many untrained industrial doctors might succumb The statutory examination of young persons encourages this type of examination and is in need of review Where medical examinations are needed they should be carefully devised to achieve the desired end, and modern methods and laboratory aids should be fully used

Industrial medicine is ready for its next step forward Further development, however, must be related to real needs, these must be assessed particularly as they concern the small factory Immediate development might well deal with some of the clearly defined needs—namely, industrial hygiene services and appropriate laboratories, a review of the duties of the appointed factory doctor and his training, a strengthening of the medical inspectorate of factories with perhaps the formation of an industrial nursing section, and further encouragement of voluntary services with emphasis on the appointment of doctors who have had some training for medical work in industry

Reviews of Books

Social and Medical Problems of the Elderly

Kenneth Hazell, M R C P , D P M , consultant gerontologist to Wolverhampton and Walsall London Hutchinson 1960 Pp 216 30*s*

This book aims to survey the medical and social issues raised by the increase in the number of elderly people in our midst Dr Hazell writes as a geriatric physician working in hospital, and he rightly emphasises the importance of an effective geriatric unit as the cornerstone of all the complex arrangements in and out of hospital which the care of the elderly involves

About half the book is a description of the organisation, structure, and function of an effective geriatric unit, and this section evidently owes much to the work of the late Oscar Olbrich There is a chapter on some of the clinical problems that commonly arise in a geriatric unit, and another on the medical care of the elderly at home The medical part of the book is set against the background of the social questions of old age, and is vividly illustrated by the author's experiences on domiciliary visits Finally there is a good picture of the social services at present available to help the elderly

Dr Hazell rightly feels that a greater proportion of our medical and financial resources should be devoted to the elderly, and the book ends with some important recommendations He advocates the provision of subsidised milk and food for the elderly, as is now done for children and expectant mothers He feels that the home-help service should be reorganised as a national service, and he wants a subsidised laundry service for the incontinent, and a national chiropody service A number of sensible recommendations on housing policy are designed to ensure that rehousing schemes do not increase the isolation of old people These views should be carefully considered—and if accepted, they will keep the nation busy for the next twenty-five years

No book gives a better picture of the problems of the elderly, and Dr Hazell is to be congratulated on his achievement, which will undoubtedly help all who are trying to ensure that the elderly in our society get a better deal than they have had in the past

Clinical Medicine and the Psychotic Patient

Otto F Ehrentheil, M D , physician, Veterans Administration Hospital, Bedford, Mass , Walter E Marchand, M D , chief, medical and surgical service, Veterans Administration Hospital, Bedford, Mass Springfield, Ill Charles C Thomas Oxford Blackwell Scientific Publications 1960 Pp 383 86*s*

The difficulties of early diagnosis and effective treatment of serious illness in the disturbed or stuporose patient are well illustrated by the authors' finding that only 1 in 5 myocardial infarctions in psychotics presented with pain This welcome and readable book deserves wide study Fourteen contributors have pooled much experience from a V A hospital of some 1800 beds, about 80% of them filled with schizophrenics, and they have gathered a useful list of transatlantic references

On the general clinical problems and on diseases peculiar to psychiatric hospitals, the book is of great practical help, but it sometimes seems that the authors have been more concerned with fitting their journal reprints into the framework than with planning a coherent textbook This seems to have been a particular impediment in some sections on organic brain disease, which include a long irrelevant statistical chapter on G P I (with no clinical descriptions) but no mention of accidental injury or E E G findings The frequent case-reports are often helpful but in the section on poisoning they add little to a poor account (which makes no mention of bemegride) The problem of suicide is dismissed too briefly, and the authors do not refer to the continuous bath in discussing the prevention of collapse during hyperactive behaviour, though they give 5 pages to an account of the only case ever reported of " heat pyrexia " during such hydrotherapy Again, a long and rather out-of-date account of the theory and complications of insulin-coma therapy contrasts oddly with the complete neglect of the dangers of electroconvulsion therapy But much of the book will be found very useful and as relevant in Birmingham as it is in Boston

Modern Trends in Urology

2nd series Editor SIR ERIC RICHES, M C, M S, F R C S, surgeon and urologist, Middlesex Hospital, London London Butterworths 1960 Pp 287 70*s*

IN recording the further advances in the specialty during the past seven years, Sir Eric Riches has had the aid of 26 famous contributors, writing with authority on the developments with which they have personally been closely concerned Recent work on biochemical aspects of renal disease, and indeed the advances made in medical urology as a whole, are properly recognised This section of the book, with the chapters on the artificial kidney, renal transplantation, and the surgical treatment of renal hypertension, will appeal to medical readers in general, and should finally disabuse them of the view that urology is an unprogressive " watertight " surgical specialty Much of the remainder is devoted to recent developments in radiological and surgical techniques, including a number of sections on the use of the intestine as a urinary receptacle or conduit The balance between technical attainment and clinical interest is, however, carefully preserved by a series of informative articles on supervoltage X-ray therapy in cancer of the bladder, chronic prostatitis, and nuclear sexing in relation to male infertility, and there are important chapters on granulomatous prostatitis and new growths of the testis

It is a pity perhaps that, after this long record of achievement within so short a time, no further pronouncement on the status of urology in relation to general medicine and surgery has been attempted Nevertheless, the progress of the specialty is amply described, and the quality of production and contents of the volume will go far towards enhancing its rapidly increasing reputation

The Integrity of the Personality

ANTHONY STORR, M R C P, D P M London William Heinemann 1960 Pp 174 15*s*

THIS interesting attempt by a Jungian analyst to define the basic hypotheses of psychotherapeutic practice is refreshingly free from condemnation of other schools, and his emphasis on the beliefs shared rather than the areas of controversy is right for a book intended for the lay public He deplores the tendency of analysts to form esoteric groups, and also the way in which an edifice of thought like psychoanalysis can become a closed circle of ideas in which every observation is referred to an existing hypothesis without ever questioning the hypothesis itself Throughout, the patient is considered as an individual personality and the analytical process is regarded as a maturing relationship—a microcosm reflecting the macrocosm of the patient's relationships in the world outside the consulting-room Many will agree with Dr Storr's rejection of the idea that the patient improves by discovering the truth about himself—there are far too many " truths " for this to be credible

St Peter's Hospital for Stone, 1860-1960

Editor CLIFFORD MORSON, O B E, F R C S Edinburgh E & S Livingstone 1960 Pp 64 21*s*

THE late Mr Swift Joly remarked of St Peter's Hospital that it was the only such institution called after a saint with a name which indicated its special work Nowadays the connection is rather a tenuous one, but a hundred years ago calculous diseases of the urinary tract were common in this country, and were increasing Their prevalence has been attributed to the monotonous and defective diet of the poorer classes during the " Hungry Forties " and the years that followed

In 1860 the hospital was opened to make generally available the recently developed techniques for removing bladder stones by methods short of lithotomy It was one of some twenty-five special hospitals which sprang up in London between 1850 and 1870, and which reflected the development of specialist trends in medicine and surgery But the innovation such institutes represented did not pass unchallenged Many attacks were directed against them (notable by Hastings' newly founded British Medical Association) and several doctors had to choose between an allegiance to an established general hospital, and to one of the new ones (In the case of St Peter's, Dr Thudichum and Mr Coulson were subjected to such pressure, and elected to resign from, and to remain at, the hospital, respectively)

Mr Clifford Morson has marked the centenary of St Peter's by writing a brief history of the hospital, to which are appended biographical sketches of each of the colourful personalities who were on its staff Sir Peter Freyer, in particular, is dealt with at some length, and those who know him only as the originator of an operation can now read of his feud with Moynihan, his private collection of prostates removed from notable patients, and of his theatre commentaries delivered in French and Hindustani alternately The hospital of the Crossed Keys may be a young one by London standards, but it has a fascinating story, which has been very well told

The Practitioner's Handbook (London Cassell 1960 Pp 711 63*s*)—This is a collection (edited by Dr W A R Thomson) of over 250 articles which have appeared in *The Practitioner's* Revision Corner since 1946 There are almost as many authors as articles, most of which have been recently revised, so that none seem dated They are arranged to cover the life of man from conception onwards Obstetrics, gynæcology, and pædiatrics claim a large share, in keeping with their importance in general practice Skins, eyes, E N T, and orthopædics all have their place, and geriatrics is properly represented The printing and layout make the book a pleasure to eye and hand, and the price is modest The articles are never more than two or three pages, so the book is well suited for reading at the odd moment No practitioner will regret buying it

Recent Advances in Biochemistry (4th ed London J & A Churchill 1960 Pp 301 50*s*)—The last edition (by Prof J Pryde) appeared in 1931, and this is in fact an entirely new book by Prof T W Goodwin He has chosen eight separate themes of current interest oxidative phosphorylation, carbon-dioxide fixation, and the biosynthesis of phospholipids, of the aromatic and heterocyclic ring compounds, and of nucleic acids and terpenes Finally he discusses the underlying mechanism, other than hormonal and neural, by means of which the metabolic activity of the cell is thought to be regulated The presentation is clear, concise, and up to date, and in character might be likened to a series of lectures suitable for honours students of biochemistry, though others wishing to keep in touch with current progress in these rapidly expanding areas will find the book a useful guide, which includes a good range of references to recent publications in the selected subjects

The Care of Invalid and Crippled Children (London Oxford University Press 1960 Pp 158 8*s* 6*d*)—This paperback, edited by Dr A White Franklin, is published for the Invalid Children's Aid Association, and they are to be congratulated for thus bringing up to date their earlier booklet of 1938 Its aim is to instruct social workers, health visitors, and school nurses in the aims and limitations of treatment for the handicapped child Dr White Franklin has chosen a good team, and the selection and presentation of topics are excellent Doctors and medical students will be exceptionally well informed if they find nothing to learn from this book, and it could not be bettered as an introduction to conditions seldom seen in the acute pædiatric wards but of great difficulty and importance in practice Why, though, is it assumed that the readers of books like this are unable to use a library? Authors are quoted in the text but there are no references

THE LANCET

LONDON 31 DECEMBER 1960

Postoperative Thromboembolism

OR should it be "operative" thromboembolism? Though the distinction is more than academic, few have quibbled about it in the past. To most surgeons deep-vein thrombosis and its sequelæ remain the postoperative complications par excellence, with enforced immobility, a restricted diet, and fluid imbalance as potent ætiological factors. So they are, of course, but more and more evidence points to the operation itself, and certainly to the day of operation, when the chain of events leading to the clinical syndrome is set in motion. SHARNOFF,[1] at Mount Vernon Hospital, New York, has studied blood coagulability in 41 patients undergoing extensive surgery, and in all he noted an abrupt rise in platelet-count and a shortening of clotting-time within a few hours of the start of the operation. Both parameters tended to return to normal a few hours later, though in some patients a second (less distinct) thrombotic phase developed in the first postoperative week. These changes were considerably smaller under spinal than under general anæsthesia, and they were most striking in two patients who died on the second and on the twelfth postoperative day. In the first (who died from massive pulmonary embolism) the platelet-count rose from 220,000 to 370,000 per c.mm. and the preoperative clotting-time of $4^1/_2$ minutes was halved during the operation. In the second the platelet-count rose from 187,000 to 418,000 and the clotting-time dropped from $6^1/_2$ to $3^1/_2$ minutes, and, though a review of the anæsthetic record showed no rise in pulse-rate or fall in blood-pressure during the comparatively uneventful colectomy, necropsy revealed an approximately 12-day-old myocardial infarct.

Though platelets themselves probably play an important part in the initiation of intravascular clotting,[2 3] SHARNOFF and his associates believe that the rise in platelet-count may be a reflection rather than the cause of the increased coagulability.[4 5] They picture megakaryocytes being carried by the venous circulation from the bone-marrow to the lungs and pounded up under the impact of the right ventricle in the pulmonary capillary bed. Whereas in normal lung-tissue sections from several species they found 2–3 megakaryocytes per sq. cm., both in laboratory animals and in patients who had died during or immediately after an operation the number of these cells was increased tenfold or more. Disintegrating megakaryocytes are also thought to release large quantities of polysaccharides,[6] and the Mount Vernon Hospital group suggest that these rather than the platelets may be the chief agents of the increased tendency to clot. Though many experimental and theoretical gaps remain to be filled (most circulating polysaccharides seem to have anticoagulant rather than clotting properties), the concept brings into focus at least three easily overlooked aspects of thromboembolism. First, deep-vein thrombosis is not the only manifestation of the surgical thrombotic state: arterial (cerebral, myocardial) thromboses may be less common, but they are no less dangerous. Secondly, of VIRCHOW's ætiological triad, qualitative blood-changes are at times the most crucial.[7 8] Thirdly, these changes—ill understood though they still are—reach their peak during rather than after an operation. These observations have the most direct bearing on the management of patients undergoing elective surgery, for—though thromboembolic disorders associated with operations, trauma, childbirth, and certain medical conditions probably have a very similar ætiology—no other group offers at present wider scope for judicious prophylaxis.

Postoperative anticoagulant therapy has now had an extensive trial on both sides of the Atlantic, and many doubters will have been converted by the controlled investigation of SEVITT and GALLAGHER at the Birmingham Accident Hospital.[9] In the light of SHARNOFF's findings it is interesting to note that many of their patients were started on phenindione before the operation (though not, of course, before the accident) and that none appeared to be the worse for it. Critics of vein ligation have argued that the method is like bolting the door after the horse, but perhaps a similar objection could be raised against instituting anticoagulant therapy after the operation, and especially after symptoms and signs of thrombosis (such as they are) have become manifest. Though we should like to know more about the chemistry and pharmacology of the perioperative thrombotic phase—especially about the effect of various anæsthetic drugs on natural and therapeutically administered anticoagulants—it may be hoped that selective anticoagulant prophylaxis will eventually supplant postoperative treatment.

Unlike anticoagulants, vein ligation has never gained wide support in this country, but it retains a rationale of compelling directness and simplicity. If a clot in a peripheral vein represents a potential pulmonary embolus, interruption of the venous channel should eliminate this hazard. Strong arguments can, of course, be advanced against such reasoning—including the possibility that the ligature itself may become the starting-point of a proximal thrombus[7]—but disfavour has always been emotional rather than rational. To some surgeons a pulmonary embolus is still a Stroke of Providence (as was wound infection a hundred years ago), and operative interference seems to them futile to the point of blasphemy. Even the most ardent advocates of the method now recognise it as a rearguard action in battles already lost, but indisputably it can save lives when showers of emboli throw an increasing strain on the right heart or when heavily infected particles are discharged from a septic peripheral focus[10] The optimal site of ligation remains debatable, but, as regards collateral circulation as well as effectiveness as a barrier to the lungs, tying the inferior vena cava has advantages which often outweigh the extra risks[11] Whatever the site, vein ligation is not an alternative but a supplement to effective anticoagulation[12]

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[2] Pennington, J. L., Prunty, F. T. G. *Brit. J. exp. Path.* 1946, 27, 200.

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[5] Sharnoff, J. G., Bagg, J. F., Breen, S. R., Rogliano, A. G., Walsh, A. R., Scardino, V. *Surg. Gynec. Obstet.* 1960, 103, 469.

[6] Ro[illegible]ard, B. *Scand. J. clin. Lab. Invest.* 1958, 10, 216.

[7] Wessler, S., Deykin, D. *Circulation*, 1958, 18, 1190.

[8] *Lancet*, 1959, ii, 1014.

[9] Sevitt, S., Gallagher, N. G. *ibid.* p. 981.

Though we now recognise thrombolysis as a physiological process complementary and comparable to (and no less important than) clotting, fibrinolysin is still the dark horse in the therapeutic field Its inactive precursor, " plasminogen ", has now been highly purified[13 14] it has a molecular weight of 83,000, and it behaves as a homogeneous material electrophoretically and on ultracentrifugation In vitro it seems to have a dual function as " proactivator " and " proenzyme " when the molecule is activated non-specifically—e g , with trypsin —its proactivator activity declines pari passu with the increase in plasmin concentration and the lysis of the fibrin substrate Testing the enzyme on dogs, FREIMAN et al[15] have demonstrated its powerful lytic effect on experimentally induced clots, especially when the material was introduced through a catheter close to the thrombosed segment They believe that previously reported differences between the behaviour of arterial and venous thrombi can be accounted for by variations in the number of collateral channels capable of delivering the enzyme to the clot[16 17], but they have confirmed the decisive influence of the age of the thrombus on the speed of lysis[16–18] It has been suggested that clot dissolution in vivo must be prepared by the penetration of a fibrinolytic enzyme (" activator complex ") into the thrombus, where it will function only after it has activated a proenzyme (" profibrinolysin ") intimately bound to fibrin[17] (The hypothesis thus implies distinct fibrinolytic and thrombolytic processes) Endothelialisation and invasion by fibroblasts of a clot could offer strong resistance to adsorption and diffusion, but even at an earlier stage molecular changes in the fibrin polymer of the thrombus might diminish the effectiveness of the intrinsic profibrinolysin or the rate of diffusion of the activator complex Of great clinical interest is the further observation of FREIMAN and his colleagues that experimental clots could not be induced or maintained for long in the presence of a high fibrinolytic activity in the blood Despite the imprecision of our methods of diagnosing venous thrombosis, and a considerable overlap between the fibrinolytic activity of anti-inflammatory agents and the anti-inflammatory effect of specific fibrinolysins, a few clinical trials[19 20] have encouraged the hope that fibrinolysin, too, may prove a useful prophylactic as well as therapeutic weapon

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[10] *ibid* 1957, i, 595, and Crane, C *New Engl J Med* 1960, 262, 947
[11] Mozes, M , Adar, R *Surgery* 1960, 48, 879
[12] Fuller, C H , Robertson, C W , Smithwick, R H *New Engl J Med* 1960 263, 983
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[16] Cliffton E E *Ann N Y Acad Sci* 1957, 68, 97
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Life at High Altitudes

AFTER a slow ascent to 25,000 feet man can survive for a while without additional oxygen and can do a moderate amount of work Some animals can live at 28,000 feet for about a week, after which deterioration sets in rapidly At the more modest altitudes of 14,000–15,000 feet (barometric pressure 450 mm Hg or less) many men spend their whole lives from infancy to death, growing, working, and reproducing normally This demands a high degree of adaptation, which is accomplished by means still not fully comprehended Anyone in normal health who ascends rapidly to these heights finds on arrival that he cannot exert himself without severe dyspnœa, and all newcomers are warned that for the first half-day or day they should go up hills or stairs very slowly lest they fall unconscious, or, better still, rest completely for six to twelve hours Thereafter most people find that they can undertake reasonable exertion without ill effects The longer the stay at altitudes which are not excessive, the better the adaptation Clearly domestic animals adapt as well as man the mule works hard, small pigs, ducks, and hens abound, and the local dog chases cars, barking the while, as fast as any of his sea-level cousins The llama of the Andes is in a special position since it retains its fœtal-type hæmoglobin

The immediate response to a fall in O_2 tension is an increase in ventilation-rate, and this is almost certainly mediated by the chemoreceptors of the carotid bodies, which have been shown to be especially sensitive to a fall in pO_2 The greater ventilation will expand the lungs more than usual and thereby provide a greater surface for oxygen absorption The increased ventilation will at the same time bring about greater than usual loss of CO_2 from the lungs Within a few hours the resulting alkalosis is corrected by the kidneys, so that there is then no alkalotic inhibition of the respiratory centre to the chemoreceptor drive[1] Alveolar ventilation is usually at its greatest in three or four days, after which it begins to fall as adaptation sets in Naturally an alteration in ventilation demands some cardiovascular adjustment, and initially the pulse-rate increases somewhat, but in about a week this has returned to the normal sea-level value, and later it may fall even lower Once acclimatisation is complete the heart responds to reasonable hard work in exactly the same way as it does at sea-level[2] This is possible because of the adjustments which take place in the blood, in the vascular supply of the tissues, and probably also in the chemistry of the tissues[3] After full acclimatisation there is a striking increase in blood-volume—by as much as 25%—and this is entirely due to an increase in the number of erythrocytes As a result the O_2-carrying power of 1 ml of blood becomes as great at 15,000 feet as at sea-level The increase in blood-volume and (since the volume increase is due to cells and not plasma) in viscosity demands further changes if the heart is to be spared an intolerable burden There is a great opening up of capillaries in the tissues with the result that the peripheral resistance falls It is not known whether this change is brought about by the hypoxia or by the raised blood-volume The increased vascularity has the added advantage that the distance across which oxygen must diffuse to reach the tissues is reduced

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[1] Stickney, J C , van Liere E J *Physiol Rev* 1953, 33, 13
[2] Korner P I *ibid* 1959, 39 687
[3] Reynafarje, B International Congress of Physiological Sciences, Symposia and Special Lectures, Buenos Aires, 1959

Possibly the opening up of the small blood-vessels in the heart, lungs, central nervous system, gut, and skeletal muscle more than compensates for the increase in blood-volume, as it has often been observed that the resting blood-pressure is lower than at sea-level The coronary circulation is thought to be particularly sensitive to slight hypoxia, and this is probably one of the most important ways in which the size of the coronary vessels is regulated at any altitude the hypoxia developing on arrival at a height will greatly increase the blood-supply to the heart-muscle and thereby prevent heart-failure in the early days before acclimatisation is complete The cerebral circulation is as sensitive to hypoxia as the heart, if not more so The mechanism of this sensitivity is ill understood, but is possibly related to a change in glycogen metabolism [2]

The need for facilitation of O_2 diffusion in the lungs makes a special demand on the right side of the heart, and, as a result, in those living permanently at high altitudes the right ventricle hypertrophies and the electrocardiogram shows characteristic features [4] The lungs seem always to contain more than the usual volume of blood, and there is constant moderate pulmonary hypertension, which contrasts with the somewhat low systolic and diastolic pressures in the systemic circulation [4] By the time adaptation is complete a resident has lower alveolar ventilation-rate and arterial pO_2 values, as well as higher CO_2 values, than a moderately acclimatised newcomer This is possibly related to the polycythæmia which is present in the resident,[2] and which is an extremely important factor in adaptation It is only of late years that some information has come to hand as to the cause of the polycythæmia It has always been suspected, on *a priori* grounds, that hypoxia was the special stimulant to the blood-forming organs, moreover hypoxia is a common factor in many conditions in which the reproduction-rate of red blood-cells is increased—for instance, severe hæmorrhage and anæmia On the other hand, a long-persisting small blood-loss also has this effect, and hæmorrhage is a more effective stimulus than *moderate* hypoxia, perhaps because of the hyperventilation and alkalosis which accompany the former Cobalt is another stimulant to red-cell formation, particularly after hæmorrhage or at high altitudes Whatever the mechanism, the result is the appearance in the circulation of a substance which, transferred to normal animals and man, displays hæmopoietic activity The substance seems to be protein and is fairly heat-resistant. It may be an α-globulin which is associated with an active polypeptide grouping On injection the substance rapidly disappears from the circulation owing to its clearance by the liver and blood-forming organs It is not quite certain where the material comes from—possibly the spleen and kidneys A very similar substance can be recovered in greater than normal amounts from the blood of patients with cardiac or pulmonary disease [5] The hæmopoietic substance seems to act by increasing the rate of red-cell formation and maturation besides hastening the release of the cells from the blood-forming organs

Even at moderate altitudes, such as 7000 feet there are measurable signs of adaptation [6] and these will be helpful in adapting to a greater height It has not been explained, however why repeated short exposures to real or simulated great altitudes lead to a remarkable conditioning, so that far greater heights than usual can be tolerated and acclimatisation is hastened Like the healthy adult, the newborn babe or animal adapts easily to low O_2 tension, but the growing child has greater difficulty The newborn has an advantage because it has for some months had greater difficulty than the adult in obtaining its oxygen, and has become adjusted to the situation The fœtus and neonate have an oxygen-dissociation curve which is shifted to the left—i e, the blood reaches a relatively higher O_2 saturation at low O_2 pressures In addition, the neonate has a right-ventricular preponderance somewhat similar to that of the altitude-acclimatised adult In the infant born at high altitude this preponderance persists, together with other fœtal features, such as narrow pulmonary arteries and arterioles whose media is thicker than normal These last items may well have some connection with the high pulmonary arterial pressure and the interesting fact that a patent ductus arteriosus is not uncommon in those who have lived all their lives at high altitudes In the normal infant at sea-level the ductus closes anatomically in the 4th month, but, if in the early days after birth the infant is made moderately hypoxic, the pulmonary arterial pressure rises rapidly and the right-to-left shunt through the ductus arteriosus is re-established [7] So far as is known, adaptation to high altitude is completely reversible on return to sea-level

Some interesting observations have been made in the high Andes on the health of the residents and the diseases to which they are inclined Coronary thrombosis and myocardial infarction are rare in all races Residents, besides having low systolic and diastolic pressures, seem to have a reduced incidence of vascular sclerosis in relation to age The blood-cholesterol is within normal limits Operative procedures for the correction of patent ductus arteriosus, and thoracic surgery in general, carry even less risk than at sea-level, thus showing one of the advantages of adaptation to hypoxic conditions Cholecystitis and cholelithiasis appear to be fairly common, despite the frequent finding of hypochlorhydria and achlorhydria, peptic ulcer is often found It is not known whether this fact is related to the observation at sea-level that peptic ulcer and polycythæmia are commonly associated with each other [1]

Occasionally the resident at high altitude may lose his adaptation and develop a condition known as chronic mountain sickness [4] This may happen at any time of life from childhood to old age, but is commonest in young adults The number of red blood-cells increases greatly, bone-marrow becomes hyperactive, and plasma-volume decreases In consequence the blood viscosity is high The right heart is unusually hypertrophied The arterial oxygen saturation is below, and perhaps far below, that which corresponds to the altitude at which the patient lives This change is paralleled by a low alveolar O_2 tension, which seems to be due to relative hypoventilation, even though the total pulmonary capacity and residual air are not significantly different from normal X-rays suggest that there may be ill-defined fibrotic changes in the lungs which may persist even after recovery at sea-level [8] On the other hand, there is some evidence that the sensitivity of the respiratory centre to CO_2 is decreased, and the administration of O_2 together with CO_2 does not alter this decreased sensitivity, which is possibly due to chronic hypoxia The chronic hypoxia may account also for the excessive polycythæmia, which is not identical with polycythæmia vera since, for one thing, in chronic mountain sickness there is no rise in the white-cell count [8] Chronic mountain sickness is cured by removal of the patient to sea-level There appears to be an undefined link between hypoventilation, hypoxia, and polycythæmia, these three signs are all found in some very obese patients at sea-level [9] Perhaps closer study of residents at high altitudes, either when well or when ill, could furnish information important not only for themselves but also for those at sea-level

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Annotations

REASSURANCE ABOUT RADIATION HAZARDS

SINCE the Medical Research Council's first report [1] on radiation hazards four years ago, tremendous research activity has uncovered many new data about how much nuclear and allied radiation man is exposed to and how it may affect him and his descendants The second report,[2] published last week, is therefore able to tackle many questions from a much surer basis of fact, though some of the fundamental uncertainties about the significance of radiation have persistently failed to resolve themselves, despite worldwide scrutiny We are now much better equipped to judge the quantities of ionising radiation to which individuals and populations are exposed from various sources, and progress in this work has been remarkable Inevitably, less has been achieved in the more exacting inquiry into how ionising radiation can affect health

Notable changes of thought have been provoked by new observations Formerly it was believed that an individual exposed to a high dose of radiation carried for his lifetime thereafter a heightened risk of leukæmia But changes in the leukæmia-rate among those exposed to the bombs of Hiroshima and Nagasaki and among those irradiated in the treatment of ankylosing spondylitis encourage the M R C Committee to " assert with some confidence that the risk of leukæmia following irradiation will decline after the lapse of a decade " Again, it used to be held that the biological effects of a given amount of radiation were the same whether it was received slowly or quickly Now recent work on somatic effects of radiation on mice suggests that a dose given over a long time has less effect than the same " acute " dose These observations accord with the earlier findings that genetic damage is similarly related to dose-rate [3] This change of opinion, therefore, puts more emphasis on the sudden doses of medical radiology (lately the subject of the Adrian report [4]) and less on the much slower exposure to background and fallout radiation These are as yet experimental findings only, but, if they prove to be applicable to man, previous estimates of the genetic and somatic damage that might be expected, for example, to follow exposure to fallout debris may be too high This reservation applies to the estimates made by the United Nations Scientific Committee [5] in 1958

In its comments on strontium 90 the report refers to the important finding that the uptake of the isotope by the roots of plants, the magnitude of which is related to the total accumulated fallout remaining in the soil, is at present of minor significance compared with the direct uptake by the parts of the plant which are above ground This uptake depends on the rate of fallout rather than on the accumulated total Thus the amount of strontium 90 eventually deposited in bone will be related to the current rate of fallout, and, as this rate has decreased appreciably since it reached a peak in 1959, these findings are reassuring and would also mean that the U N figures were too high Moreover, the reservoir of fission products in the stratosphere is smaller than was estimated previously [6] The report concludes that " the average levels of strontium 90 which have been observed both in the diet and in human bone in the United Kingdom are such as to make it extremely unlikely that there has been any appreciable hazard to human health from this isotope "

In 1956 the M R C Committee set the maximum allowable bone concentration of strontium 90 in the general population at 100 $\mu\mu$C per g of calcium, and they set a warning level of 10 $\mu\mu$C It is now fairly certain that strontium will not go on building up in bone for a long time after fallout has decreased (that there will not be a big " overswing"), and for this and other reasons permissible and " warning " levels have been revised The whole-population figure has been brought *down* to 67 $\mu\mu$C per g to fit in with a recommendation of the International Commission on Radiological Protection, but the warning level has been relaxed to half this—i e , 33 $\mu\mu$C

Another key figure in the report is the estimate of gonad dose from fallout, which is a measure of the genetic consequences of nuclear explosions, this is put as 1 2 mrad per year (averaged over a 30-year period), compared with the 19 mrad from medical radiology, as judged by the Adrian Committee, and the 85–106 mrad from natural background

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[1] The Hazards to Man of Nuclear and Allied Radiations Cmd 9780 H M Stationery Office, 1956

[2] The Hazards to Man of Nuclear and Allied Radiations A Second Report to the Medical Research Council Cmnd 1225 H M Stationery Office 1960 Pp 154 7*s*

[3] See *Lancet*, 1959, i, 85

[4] Radiological Hazards to Patients H M Stationery Office, 1960 See *ibid* Dec 10, 1960, p 1285

[5] See *ibid* 1958, ii, 355

[6] See *ibid* Dec 17, 1960 p 1337

PRUNING THE COST

SINCE the National Health Service began, except for a brief period in the early '50s, the drug bill, like most other bills, has risen. In 1949, the average cost of the general practitioner's prescription was around 3s., by 1956 it had reached 5s., and for August, 1960, the figure was almost 7s. 2d. Successive Governments and their successive Ministers of Health have tried several means to curb this apparent inflation: pharmacists' "on-cost" or profit margin was cut, a levy of 1s. on each prescription form was introduced, and later this was increased to 1s. per prescription. The Hinchliffe Committee[1] considered the problem for over two years, the Cohen Committee examined the clinical advantages of thousands of proprietary preparations against their more moderately priced official equivalents, but the price still rose. The rise in cost was accompanied by an increase in the proportion of proprietary drugs and preparations prescribed, partly because more efficient antibiotics and other specific remedies became available, and partly because more proprietary preparations were marketed and became the success measure of their makers' marketing.

Not unnaturally, therefore, the Minister sought to establish some measure of control over the price of such preparations. In 1957, agreement was reached with the Association of British Pharmaceutical Industry on certain cardinal principles: prices in Great Britain were not to exceed those obtained in the export market if more than 20% of the product was shipped abroad; for preparations which had a standard equivalent the proprietary should not cost more than the official preparation; for other preparations a formula was agreed for determining a maximum price. Perhaps most important from the manufacturers' point of view, it was agreed that price control should not be applied during the first three years of a product's life, to enable the manufacturer to recoup his research and development expenses. The original scheme, which the Ministry believes has worked well, but which has been the target of the Public Accounts Committee,[2] came to an end this month, and the Minister of Health recently announced some important modifications.[3] The most important, and most rational, is that the three-year period of grace for manufacturers introducing a new product will no longer apply if the product owes nothing to fresh research. This restriction should restrain the exuberance of those producers who seize upon the research work of others, or who merely make minor variations, extending to little beyond packaging or flavour, of well-tried pharmacological combinations. The Ministry, too, may now enter into direct price negotiations with firms which produce drugs protected by patent rights and so are the subjects of a virtual monopoly, for these there may be no competitive export price. To qualify for the export test now, 25% of total output must be sent abroad, although 20% will be accepted if only one of the firm's products is exported in substantial quantities.

Since the cost of the pharmaceutical service has not been going up at a much greater rate than other Health Service costs—or the price of other commodities—some manufacturers may feel that too much is being made of an item that accounts for some 7% of the total expenditure of the Health Service. Certainly, the Hinchliffe Committee declared that the community as a whole derived tremendous benefits from the pharmaceutical service financially as well as in the relief of suffering and the saving of life and that it had relieved the pressure on expensive hospital accommodation, and the committee urged the Minister to consider ways and means of publicising these facts in a telling way. Nevertheless, the significance of the rising drug bill will remain hard to assess until we have more information about the proportion of the manufacturers' turnover that goes into research, compared with what is spent on promotion, advertising and distribution. Meanwhile manufacturers must expect their lavish advertising outlay to be widely construed as adding too much to the drug bill.

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[1] See Lancet 1959, i, 1027.
[2] Ibid 1960, i, 343.
[3] Ibid Dec. 24, 1960, p. 1404.

HYPOPHYSECTOMY

WHAT we should like to know about complete hypophysectomy is not only how to achieve it but whether its achievement is desirable. Consideration of anatomy suggests that cutting the stalk at a low level and removing the central portion of the gland will abolish all the normal blood-supply to the pituitary, but whether any further destruction is necessary is not yet certain.

Notter[1] has treated 49 cases of mammary cancer and 6 other cases by implanting into the pituitary small spheres containing radioactive yttrium (^{90}Y). Radioactive yttrium was first implanted into the pituitary several years ago.[2]

By Notter's technique 20–30 spheres each 1·2 mm. in diameter and with a total activity of 2·5–3 mC, are implanted into the pituitary by the nasal route with the aid of Riechert's stereotaxic apparatus[3,4] and of screening with image intensifiers. (The operator with all possible precautions receives 25 mrad. per implantation on the face and hands.) The half-life of the yttrium is 61 hours, the emission being almost pure β-radiation with a half-dose depth of 1 mm. Radioactive impurities are negligible. The cluster of spheres gives 100,000 rad. at 3 mm. from the surface—a dose which probably just causes necrosis in the gland. Surrounding structures are more sensitive, except the carotid arteries which are highly resistant.

In 80% of the cases the pituitary was completely destroyed. The operative mortality was 9%. In some cases the chiasma, optic tracts, and oculomotor nerves were damaged owing to misplacement of the spheres too high or too laterally. In 18 cases rhinorrhœa ensued, in 8 of these cases meningitis developed, and, of these 8 patients, 2 died. (In the latter part of the series the implantation channel was blocked with a screw, in order to reduce the risk of rhinorrhœa.) Polyuria developed in 49 cases.

No simple hormonal estimation distinguished partial from complete destruction, but complete destruction was associated with absence of gonadotrophins 1 month after implantation. Functionally complete "depression" of the pituitary was assumed if, in addition, the 24-hour radioiodine uptake was below 15% at 1 month, and protein-bound iodine below 4 µg. per 100 ml. at 3 months, after implantation. No correlation could be detected between hormone treatment, hormone excretion, or the age of the patient on the one hand and tumour response on the other. Complete destruction of the pituitary was apparently not essential for palliation: the pituitary was probably not completely destroyed in 4 out of 16 cases in which the tumour regressed The pharyngeal hypophysis contained differentiated eosinophil and chromophobe cells whenever the intrasellar gland had been damaged by irradiation, but when the gland remained intact, only undifferentiated embryonic cells were found

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[1] Notter, G. Acta radiol., Stockh. 1959, suppl. 184.
[2] See Lancet 1959, ii, 833.
[3] Riechert, T., Wolff, M. Arch. Psychiat. 1951, 186, 225.
[4] Riechert, T., Mundinger, F. Acta neurochir. 1955, suppl. 3–4, p. 30[illegible]

Useful though these findings are, they do not answer two important questions namely, what is the least that needs to be done to the pituitary to secure the greatest possible clinical remission, and how can such remission be achieved most reliably and safely?

HÆMAGGLUTINATION IN HEPATITIS

THE failure up to now to find a laboratory animal susceptible to infection by the human hepatitis virus or a culture medium in which the virus can be propagated has seriously hampered attempts to develop a specific diagnostic test for this widespread disease The ability of certain viruses to agglutinate avian and sometimes other red blood-cells has, however, offered the possibility of a simpler alternative During infection with a hæmagglutinating virus a positive agglutination test might be obtainable with serum obtained during the stage of viræmia, while later in the course of the disease specific inhibitors might appear The success in detecting both these phases in monkeys infected with yellow fever [1] has encouraged several workers to undertake a similar study of patients with infective hepatitis The results of three independent investigations [2-4] agree broadly that in the acute phase of this disease hæmagglutinins for the erythrocytes of day-old chicks are present in the serum of the majority of patients

Since the available evidence was insufficient to establish definitely that the hæmagglutinating activity was due to the presence of the virus, Havens [5] undertook a further study of this question Because most human sera agglutinate to low titre the red cells of day-old chicks, no serum was accepted as positive unless its titre reached 1 in 80 Titres of this level and above were again found in some 70% of 95 sera from patients in the early stages of acute viral hepatitis, whereas similar titres were reached by only 9% of 108 sera from patients with chronic hepatitis No positives were found among 20 patients with hæmolytic jaundice or 59 patients with various forms of obstructive jaundice Of 104 sera from healthy persons 4 just reached the diagnostic titre

Repeated tests showed that the agglutinating titre rose for the first 10–12 days of the disease, then fell progressively and was usually negative by the end of 6 weeks At this time, moreover, the serum inhibited the activity of positive sera Unfortunately, this cannot be taken as evidence for a specific antibody, as similar inhibitory activity is found in sera both from patients with extrahepatic biliary obstruction and from those with acute hepatitis from which the agglutinating factor has been previously absorbed by chick erythrocytes

Further warning that the agglutinating activity of these sera is not necessarily due to the direct activity of the hepatitis virus comes from Havens' results with the blood of donors known to be capable of transmitting serum hepatitis Of 19 such donors only 1 gave a positive hæmagglutination test It must, however, be admitted that in several instances the donor was tested long after the blood for the suspect transfusion had been given, and the test serum had been deep-frozen for months or years—a procedure known to reduce the proportion of positive tests The development of positive reactions in the serum of 7 out of 10 volunteers who had received icterogenic material emphasises the close relation of the presence of the virus to hæmagglutination

REABLEMENT AFTER A STROKE

THE increasing incidence of cerebrovascular disease [1] has awakened interest in its prevention and treatment This interest has been encouraged by the introduction of angiography, whereby the site of strokes can be better identified,[2] and by the development of treatment by extirpation of intracerebral clots,[3] surgical relief of carotid stenosis,[4] and administration of anticoagulants [5-7]

Survivors from strokes are often disabled, and their reablement poses a considerable problem for the medical and social services This problem was discussed at a meeting convened in London on Dec 9 by the Chest and Heart Association for workers from voluntary organisations The presence on the platform of a neurologist, a geriatrician, a physical-medicine specialist, and a psychiatrist gave some inkling of the many branches of medicine involved All agreed on the need for early ambulation and for a vigorous approach to reablement, the patient being encouraged to do things for himself from the outset One step taken alone does more for the morale of the patient than ten taken with support from a physiotherapist For the best results doctors, nurses, physiotherapists, and occupational therapists must work as a team This demands careful coordination for instance, if, owing to shortage of staff and time, the nurse does a thing for the patient rather than supervise his doing it for himself, much good may be undone The services of the psychiatrist are not often sought, but his experience in recognising motivation may often be of value, especially in relation to the patient's relatives Independence, carefully fostered in hospital, may be lost when the patient returns home, if he wishes to tie his relatives securely to himself, or if they wish to expiate a guilt feeling towards him and his illness

Too often the patient who has had a stroke is regarded as inevitably unemployable It is true that many are already past the working period of their lives, but many others are not These are in general too old to justify training for a new job, but often their old job can be modified to suit their disability the hemiplegic lacks a second " holding " hand, but effective jigs can often be devised as a substitute But, though the quality of the hemiplegic's work may be unimpaired, his output is reduced Competitive industry cannot be expected to fill this gap, and there is at present no social provision for it Nor, as the numbers of these patients increase, are sheltered workshops or outwork a complete solution For many patients they are a great boon, but the aim should be to get as many patients as possible back into industry, in which they should be offered work adapted to their needs, and provided with a living wage At a larger conference planned for next year this growing problem will no doubt receive closer attention

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[1] Porterfield J S *Trans R Soc trop Med Hyg* 1954 48 261
[2] Morris J A Professional Report U S Army 406th Medical General Laboratory Tokyo 1957, p 223
[3] Havens W P, Jr *New Engl J Med* 1958 259, 1202
[4] McCollum R W Bech, V Isacson P Riordan, J T *Amer J Med* 1959, 27 703
[5] Havens W P Jr *Arch intern Med* 1960 106, 327

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[1] Elkington J St C *Lancet* 1958 ii 275 327
[2] Bull J W D Marshall, J, Shaw D A *ibid* 1960 i 562
[3] McKissock, W, Richardson A Walsh L *ibid* 1959, ii, 683
[4] Edwards, C H, Gordon, N S Rob C *Quart J Med* 1960 29, 67
[5] Carter, A B *Lancet* 1960, i 345
[6] Marshall J, Shaw D A *ibid* p 995
[7] Fisher, C M *Neurology*, 1958, 8 311

Special Articles

PREVENTIVE GERIATRICS

Opportunities of a Community Mental Health Service *

DUNCAN MACMILLAN
O B E , M D , B Sc Edin , F R C P E , D Psych
PHYSICIAN-SUPERINTENDENT, MAPPERLEY HOSPITAL,
MEDICAL OFFICER OF MENTAL HEALTH, NOTTINGHAM

IN our Nottingham mental-health service, special facilities for elderly people were first provided as a matter of expediency Some ten years ago we realised that, unless active steps were taken, the treatment units and admission wards of the psychiatric hospital would be swamped by the rising flood of geriatric admissions, especially on the female side But the work was continued and developed because it soon became clear that the maintenance of these patients in the community was also in their best interests, and that the family setting, not the hospital ward, was the best milieu for them

We can now offer our elderly psychiatric patients community care, joint medical and social domiciliary visits, outpatient services, a geriatric day-centre, day-hospital facilities, short-term inpatient treatment, and long-term hospital care From our experience of this integrated service some useful lessons have emerged

REJECTION

We see our patients at all stages of the psychotic process—in the home as well as in hospital This has convinced us that the emotional relation between the old person and his responsible relatives, friends, or neighbours and the rest of the community determines both the progress of the illness and the need for long-term admission to hospital

When the old person lives in isolation, either psychological (because of lack of interest, antagonism, self-pity, or resentment on the part of the relatives), or actual (because of solitude), deterioration sets in Old people, particularly when their mental abilities are deteriorating, are emotionally dependent on the feeling that they are still appreciated and that their existence is of value If they still feel that they are of use and of some service in the family or the community, deterioration and the development of senile psychosis advance slowly if at all Once this emotional link is lost, particularly if they realise that they are "rejected", senile psychosis develops rapidly

By " rejection " I mean the relative's determination to be free from what has become an intolerable burden This feeling takes time to develop Many relatives at first willingly and unquestionably accept responsibility for an old person because of a sense of duty But as the months and years pass, the responsibility becomes more irksome, and the restriction of pleasures, social activities, and holidays is resented—usually subconsciously at first These feelings develop more rapidly as a rule if other people are involved—e g , if children are being deprived of holidays —or if there is a grievance because other relatives are not doing their fair share If this " partial rejection " is not relieved, it crystallises into " complete rejection " A crisis is precipitated by some specific incident or accumulation of incidents—e g , anxiety over wandering, sleeplessness through nocturnal restlessness of the old person, or resentment over paranoidal accusations

Once rejection is fully established, in my experience nothing will alter it Neither short nor prolonged relief through admission to hospital is of any avail The relatives are determined not to accept any further responsibility, and will take extreme measures to avoid doing so In deciding whether to admit a patient to hospital, the relative's attitude is more important than the duration of the psychosis or the severity of the symptoms Even in a severe senile psychosis, if the relative is willing to continue to look after the patient at home, admission to hospital may not be necessary, yet it may be essential in a slight psychosis if the patient is rejected by his relatives or the community

HELP IN TIME

If adequate and timely help is given, rejection can be halted But we must be prepared to intervene much earlier than is customary

For example, where there is an atmosphere of rejection, even if it is due to physical or social causes, we have found that if no action is taken the patient will deteriorate and may well develop psychiatric symptoms which will necessitate admission to one of our units in a few months' time Now when we meet a situation of this kind we at once admit the patient to hospital for a time to prevent the rejection from growing

Often when we arrive at the home, we find that the attitude of the relatives has changed, and that admission to hospital is no longer desired Previously we would have left, and made a note " no action necessary " Now we sit down in the home and discuss the situation to see how we can give effective help and support Especially where there are children, lack of proper holidays over several years often gradually causes rejection Either the old person is taken on holiday and ruins the family's pleasure, or it is felt to be less of a strain not to go, and no holiday is taken Often relief at holiday times is all that is necessary to ensure willing acceptance of the responsibility of looking after the old person We now have lists of holiday-relief admission dates for the summer months Often the relatives contact us about the dates months beforehand so that they may make holiday arrangements and bookings

CONTRIBUTION OF THE DAY HOSPITAL

Besides providing an invaluable service for solitary old people and for those whose relatives have to go to work, the geriatric day-centre or day-hospital eases the strain in many families where partial rejection is occuring The day hospital is particularly useful for patients who improve with admission to hospital and relapse immediately on return home, to improve again in hospital, and deteriorate again on return home We now arrange for them to attend the day-centre from the hospital for the last two or three days of their stay, and then to continue to attend from home

At the relatives' reunion meetings, held in the evening at the day-centre, it is interesting to see how the lives of four or five people may benefit by the attendance of one old person at the centre

CONTINUING HELP

As part of our scheme of short-term admissions we assure the relatives that on the patient's discharge from hospital they are not expected to resume full responsibility It is made clear to them that the hospital is prepared to readmit the patient if he relapses, in a family emergency, and at holiday times On their visits the social workers encourage the family to refer their other problems to the

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* Extracts from a lecture to Canadian university psychiatric departments in March, 1960

mental-health department and to call on its staff for help in need

In the minds of most relatives there is a conflict between duty and affection on the one hand and resentment of the strain and responsibility on the other These conflicting emotions vary in degree in different countries and in different social strata When admission is requested, there is usually a strong sense of guilt at making a permanent decision about hospital stay, and relief is often expressed when admission is arranged for, say four weeks only, with the possibility of a return home in the event of improvement The feeling is deepseated, and often used to be the subconscious reason for unfair criticisms of the care and treatment of the aged person in hospital, With support, the relatives will often prefer to continue to accept a responsibility which they had begun to find insupportable It is very important that they should know that help is available in need It is the continuous long-drawn-out struggle without hope of alleviation which leads to rejection

PROPHYLAXIS

Eventually ways and means will be found to prevent premature impairment of the brain as an intellectual apparatus, and our knowledge of how to avoid pathological conditions of the cerebral vascular system will improve In the meantime there are many ways of preventing secondary emotional disabilities, which too often lead to senile psychosis and the major disabilities it brings They are a practical form of prophylaxis, for we have found that the organic intellectual deterioration is of minor importance, so long as the basic emotional needs of the old person are satisfied The aged need sympathetic companionship, appreciation, and a feeling that they are wanted and of use Their emotional needs are not usually excessive so long as interpersonal relationships are satisfactory, and the old person is usually satisfied with much less than the younger one But the minimum necessary is not available to the old person living alone—by this I mean in true isolation even from friends and neighbours It is also not available when the old person is " rejected " and has to accept that he is no longer wanted Deprived of this minimal emotional fulfilment, the old person reacts emotionally by making excessive demands, and this leads to a further deterioration in interpersonal relationships Isolation supervenes, and psychotic symptoms of antisocial attitude or withdrawal begins

The chief manifestations of what is called senile psychosis or senile dementia are not organic, they are an emotional response to unfulfilled basic emotional needs It is not the organic memory impairment, but the restlessness, the nocturnal wandering, and the incontinence which bring matters to a head The greater my experience of non-organic incontinence is, the more I become convinced that it is an emotional reaction—a protest or an expression of unhappiness or dissatisfaction

Over and over again we have found that geriatric psychiatric conditions, which used to be regarded as wholly organic and permanent and necessitating hospital admission, are in fact partly organic and partly reactive, and that the reactive symptoms are the more disabling

Observation over some years of the patients attending the day geriatric centre has shown that conditions diagnosed in hospital as senile dementia gradually improved and the patients became re-socialised Often a diagnosis of senile psychosis, made according to the usual criteria, has to be altered to that of a functional condition The functional state gradually becomes evident as the underlying cause of symptoms which are superficially those of organic senile deterioration

When the emotional needs of the old person have been unsatisfied for any length of time, senile social deterioration with subsequent onset of senile psychosis begins The time varies with the individual and with the circumstances of the withdrawal When two old people have been living together as a little isolated community of their own, and one dies, leaving the other in solitude, we have found the period to be about 4–6 months When the isolation of the old person is more gradual and he has faced no grief, the process is more gradual

Paranoidal reactions are also often reactions to loneliness and psychological isolation In folie-a-deux in geriatric psychiatry, the two people usually seem to find enough satisfaction in their joint paranoidal system not to become more than a mild nuisance to the neighbours and other people against whom the ideas are being projected Most paranoidal old people can remain in the community with the help of the social services, social education, and reasonable tolerance on the part of all concerned The geriatric day-centre is of great value in enabling them to readjust

Physical needs are also important The daily meal at the day-centre and the regular diet of the short-stay geriatric annexe together with treatment of physical disease can work wonders in changing the psychiatric picture

The atmosphere of the centre and of the inpatient annexes must be a group one, and the best number for a geriatric group seems to be 6–10 Until the group relationship had developed at our day-centre, the old people did not accept it, and persistently stopped coming on one pretext or another Once the group atmosphere was established, the whole picture changed—they were eager to come, and were disappointed when they could not If the centre was closed more than three or four days the continuity broke, and the group reaction had to be built up again For this reason the original arrangement of closing the centre at holiday-time for a week or two was discontinued, and the holidays of the staff are now staggered A sympathetic and understanding atmosphere with common activities and a regular routine are the essential for the group relationship

We hope to expand our use of prophylactic measures through the day-centre and the day hospital but some measures have already proved useful

Since we have found from experience that when one of two isolated old people dies, the other tends in a few months to develop a senile psychosis, the health visitors have been instructed to notify these cases so that the survivor may attend the day-centre From the wards of the general hospitals patients with physical illnesses and commencing reactive psychiatric states are proposed for attendance at the centre General practitioners now often refer old people before actual psychotic symptoms have developed The old people are also beginning to come themselves, and a few have called at the centre to request permission to attend, usually quite appropriately

Instead of providing more and more residential accommodation for old people it would surely be logical to provide more and more community services, day-centres, and short-stay inpatients units, so as to give expert help with potential psychiatric illness as early as possible With this help old persons can often continue to live at home, their relatives are relieved of undue strain and have their emotional conflicts resolved. A few psychiatric beds will be needed to give active short-term relief as well as some for long-stay patients But by using community methods the pressure on psychiatric beds as well as on long-stay beds for physical illness and on residential accommodation, will be relieved

The problems of old people in health, of old people with a physical illness or disability, and of old people with psychiatric illness are so closely interwoven that a joint approach by the general hospitals, the psychiatric services, the local-health-authority services, the voluntary services and the residential and community resources of the local-authority welfare service is necessary Our integrated mental-service in close association with the general hospital geriatric service and the welfare department of the local authority largely achieves this, though closer cooperation with the voluntary services would be an advantage No single approach will cope with the problem, and concerted action is necessary, especially if we are to prevent as well as treat social breakdown in the elderly

THE THERAPEUTIC VALUE OF THE ROCKING CHAIR

R. C SWAN
M B Lond
GENERAL PRACTITIONER, SUNDRIDGE, ONTARIO*

AMONG the phenomena of modern medical practice is the increasing importance of geriatrics As a result of many advances, particularly in therapeutics, people now expect to live longer than ever before and the once unfashionable diseases of the old occupy the limelight But with thickening arterial walls, tiring muscles, thinning bones, and general wear and tear, man in his seventh age slows down physically and mentally The great problem of old age is stasis All situations which contribute to loss of reasonable activity or cause immobilisation of elderly people are to be avoided The dangers of going to bed have already been officially and eloquently described Without compiling an exhaustive catalogue, some of the more common effects of inactivity can be listed as follows

Locomotor System

Muscle wasting and atrophy from disuse, stiffness of joints, osteoarthritis, musculoskeletal deformities, and generalised osteoporosis from disuse

Alimentary Tract

Loss of appetite leading to loss of weight, and to deficiencies of vital minerals and vitamins, constipation, and hernia

Urinary Tract

Cystitis and renal calculi

Respiratory System

Poor respiratory movement predisposing to infections, hypostatic pneumonia, and pulmonary congestion

Hæmopoietic System

Dyshæmopoietic anæmia and purpura, due to deficient diets

Vascular System

Arteriosclerosis, venous congestion and stasis predisposing to thrombosis, hypostatic ulcers, pressure sores in the bedridden, and dependent œdema

Mental State

Depressions, hypochondriasis, and psychoses

In those countries most concerned with the problems of an ageing population, vast sums are being spent on and in institutions for the care of the aged

As a general practitioner in North America, however, I am struck by the excellent mental and physical state of those who survey my entrance to their homes from a rocking chair For the benefit of readers unfamiliar with North American civilisation, it should be understood—Hollywood and glossy magazines notwithstanding—that in many urban and rural areas of America people live in homes mainly made of wood, with style and furnishings guided by this medium Rocking chairs are a familiar item in many homes, and far more common than in Europe In ascertaining the rocking chair's virtues various factors are involved

It enables all but the most feeble to indulge in limited exercise without regard to time or weather, and in a dignified manner

The activity imposed on forearm and calf muscles encourages venous return, and thus increases the cardiac output and circulation generally, and helps the absorption of dependent œdema

The exercise itself promotes respiration and discourages formation of hypostatic pulmonary congestion

By promoting movement it stimulates muscle tone and encourages supple joints

Towards night its repetitive and sedative effects encourage sleep The hypnotic effects of rocking in infancy are well known, but its value in the aged is perhaps less realised

"Rocking , psychoanalytically speaking, can be considered a socially acceptable and significant activity, encouraging the individual to take part in home activities and to maintain integration with other members of the family circle

Statistics are difficult to obtain on this subject, and it may be that I am mistaken in my views But they have the merit of original observations made on some forty families seen weekly in their homes in Northern Ontario, over an area the equal of Yorkshire In conclusion it is worth adding that the rocking chair is cheap and easily obtainable, has no side-effects, is non-toxic, and needs no prescription—other than the recommendation of a family doctor concerned with the health of his elderly patients

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Public Health

Scottish Vital Statistics

CANCER and diseases of the circulatory system both caused more deaths in Scotland in 1959 According to the Registrar General's report, malignant neoplasms caused 11,032 deaths, this is equivalent to a death-rate of 212 per 100,000 The standardised death-rate from cancer for men rose from 186 in 1931 to 251 in 1959, an increase of 35%, while for women the corresponding rate fell by 8%, from 182 to 168 In men deaths from cancer of the lung, larynx and buccal cavity, and, to a lesser extent, kidney, bladder, and rectum, as well as from Hodgkin's disease, preponderated, and in women deaths from cancer of the thyroid, intestine, biliary passages, and liver The mortality from cancer of the respiratory system was five times higher in men than in women

Circulatory disorders caused 23,530 deaths, 21,122 of these were ascribed to heart-disease, the majority being arteriosclerotic or degenerative lesions Deaths attributed to coronary thrombosis increased from 9923 in 1958 to 10,089 in 1959, 6411 of these were of men and 3678 of women

Deaths from all causes registered during 1959 totalled 63,061, as against 62,065 in 1958, the rate per 1000 population was 12 1 (12 0 in 1958) There were 99,251 births (99,481 in 1958), the birth-rate being 19 12 per 1000 Maternal mortality was the lowest ever recorded in Scotland—36, representing a rate of 0 4 per 1000 live and still births

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* Present address London School of Hygiene Keppel Street, London, W C 1

1 Annual Report of the Registrar General for Scotland 1959 No 105 H.M Stationery Office 1960 Pp 465 25s

Points of View

DIAGNOSTIC REASONING AND THE LOGOSCOPE

F. A. NASH
M.R.C.S.
MEDICAL DIRECTOR, SOUTH WEST LONDON MASS X-RAY SERVICE

WHAT happens in the physician's mind when he is faced with a new case? This will depend on his experience, on his book knowledge, on his mental endowment, and on the occasion.

MODES OF DIAGNOSIS

Sometimes the patient's story and the results of physical examination may bring into action the subconscious process of immediate recognition of the disease. Here the diagnosis is made in the same way as we " diagnose " the identity of our friends—without conscious formulation of reasons but with a high degree of confidence and accuracy. This capacity for recognition diagnosis is the invaluable possession of the experienced doctor.

If immediate recognition diagnosis does not take place, we may recall descriptions—from books or from memories of practice—of several diseases that might fit our patient's case. This process is not usually a logical effort, but relies on the storehouse of the memory to give out recollections of cases that have something in common with the present one. It is fallible. More is missed through not recalling, and so not looking, than through not knowing.

In other cases, we may take a main symptom or sign and, using it as an intellectual straw to which to cling in a sea of memories and observations, review the diseases that could cause it. Another mode of approach would be to consider the possible causes of *all* the patient's signs and symptoms. But at this point there are two ways in which we could proceed. Should we consider the possible causes of *each* of the patient's symptoms and signs in turn, or would we do better (if we were able) to recall the diseases which could cause the *whole group* of signs, symptoms, and other findings?

THE THEORY OF DESCRIPTION AND IDENTIFICATION

To answer these questions, consider an analogous problem presented to the police when they wish to interview suspects about a crime. Suppose that this is obviously the work of a professional. The police have an index describing all known criminals in the area. They have a description of the wanted person: " Height over 6 ft., age under 21, hook nose, black-haired, left-handed."

One approach would be to take a single attribute and to interrogate all those possessing it. Perhaps the records show that there are 100 known crooks over 6 ft. Should they all be carefully interviewed, and would this be adequate and economical? Surely it would be neither, for, taking another single attribute such as black hair, the police might find that there were 200 black-haired suspects, some over 6 ft. tall, some not. A clue to the most efficient approach is gained when we realise that while 50 men may be aged under 21, and 60 men may have hook noses, the number having both hook noses and aged under 21 (i.e., individuals sharing these attributes) will be much less—perhaps half a dozen. Furthermore, strange though it seems, the more attributes are considered together, the fewer people will be found to possess them all. By taking the attributes together, a powerful narrowing-down effect in the range of " possibles " is obtained. The aim is to increase the number of attributes in the description until the narrowing-down effect has proceeded to a point of uniqueness in which an individual is " de-fined ", distinguished, and differentiated from all the rest. It may be found that there are insufficient grounds for narrowing the possibilities to 1 person because the necessary manifestations are lacking. In that case, there will be several individuals possessing the combination of attributes. If there are insufficient grounds for the diagnosis of a single man as the chief suspect, then the police will have to make further observations (on the short list of " possibles ") to increase the narrowing effect by obtaining extra data. In this example, be it noted, the police have to rely, unless they are very lucky, on finding an individual who possesses a unique combination of non-unique (i.e., *shared*) attributes. *Individuality is a conglomeration of non-unique qualities, not a set of pathognomonic attributes.*

A disease, like a person, may be regarded as a unique combination of non-unique (i.e., shared) manifestations or attributes. Pyrexia is shared among many diseases, even as black hair is shared among many individuals. The number of people who have black hair greatly exceeds the number of people each of whom has both black hair and a hook nose. Similarly, the number of diseases in which pyrexia has been described greatly exceeds the number of diseases in which both pyrexia and cough have been described. Many diseases share the manifestation of pyrexia. Many diseases share cough. Fewer diseases share both.

Ideally, then, one should recall and review all the diseases which could cause the combination of signs and symptoms manifested by the patient—but how can we do this? We can look up the causes of single symptoms in certain textbooks but there is no index in any textbook giving the causes of individual combinations of signs and symptoms. Inspiration is not enough. Recall and review should be systematic, adequate, accurate, comprehensive, effortless, and instantaneous. Diagnosis should, like justice, be demonstrable.

DIAGNOSTIC REASONING

The majority of signs and symptoms have perhaps half a dozen causes. Others, however, may have fifty or a hundred. These form a burden on the memory. To review the possible causes of each symptom in relation to the patient's illness is time-consuming. Where a patient has two or more symptoms, each with a large number of causes, the task of logically selecting the diseases capable of causing the group of symptoms could not be done infallibly without paper and pencil, and leisure. Thus, the physician may need to solve a massive expression like:

> If manifestation alpha (e.g., a symptom or sign) has been described in diseases a, d, e, f, &c., to, e.g., 50 items, and
> If manifestation beta has been described in diseases b, e, g, n, &c., to, e.g., 100 items, and
> If manifestation theta has been described in diseases c, e, j, z, &c., to, e.g., 70 items.
> Then manifestations alpha, beta, and theta have been described in disease e, &c.

This activity may be termed the conjugation of manifestations (Nash 1959). This procedure, used at the Johns Hopkins Hospital, is described by Harvey and Bordley (1955). They list the following " steps in diagnosis ":

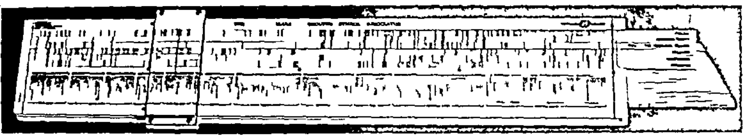

Fig 1—General view of logoscopic slide-rule

1 —Collecting the facts

- *a* Clinical history
- *b* Physical examination
- *c* Ancillary examinations
- *d* Observation of the course of the illness

2 —Analysing the facts

- *a* Critically evaluate the collected data
- *b* List reliable findings in order of apparent importance
- *c* Select one or preferably two or three central features
- *d* List diseases in which these central features are encountered
- *e* Reach final diagnosis by selecting from the listed diseases either (1) the single disease which best explains all the facts, or, if this is not possible, (2) the several diseases, each of which best explains some of the facts
- *f* Review all the evidence—both positive and negative—with the final diagnosis in mind

The process of conjugating the manifestations described earlier and advocated by Harvey and Bordley (1955) can be done with paper and pencil, but it may take up so much time as to become impracticable

LOGOSCOPY AND THE LOGOSCOPE

This work can now be done by a system called logoscopy This is a method for data access (or recall), data association, and data display Its applications are not confined to medicine The system is based on the capabilities of an instrument called the logoscope (from the Greek λόγος, meaning a thought, idea, or word, and σκοπεῖν, to regard or view) The device, currently, is in slide-rule form (fig 1) It is a panoramic combination index to textbook data it is therefore a supplement to books In principle it is a mechanical table with numerous vertical columns which are removable to allow the manipulation at will of any chosen groups of (usually) qualitative data Each vertical column is labelled with the name of an attribute—in medicine with the name of a sign or symptom These columns (called sign and symptom strips) are stored in alphabetical order in the back of the rule

Operation and Interpretation

Down its righthand face is a reference index of disease categories (337) If a single sign or symptom strip is fully inserted into the rule's face, it will be seen that the surface of the strip has its own spectrum or pattern of transverse lines There is a line at the level of each disease in which that sign or symptom has been described

If several strips (i e , an individual combination of signs and symptoms) are inserted together into the face of the rule, here and there two or more of the spectral lines will coincide so that it looks as if a single straight horizontal line has been drawn across several or all of the strips This means that these symptoms (or signs) have been described in the adjacent disease on the index scale

The face of the rule now shows in panorama the various diseases in which some or all of the inserted signs and symptoms have been described In doing so, it displays the differential diagnostic field and answers the basic question " In what diseases has this individual combination of signs and symptoms been described? " *

The physician should carefully " think his way " down the information shown on the face of the rule, and consider its possible bearing on the patient's case Used in this way, the rule suggests extra questions in history-taking, and indicates what to look for in further physical examination Thought is focused on relevant possibilities

Metaphorically, the device can be described as a diagnostic bus or street-car, not as a diagnostic taxicab The user must realise that it will often take him somewhere near his diagnostic destination, and so save him much effort, but he will not usually be taken from door to door

One must dismiss any preconceptions that the logoscope is a sort of medical Aladdin's lamp which, when rubbed, gives the user the diagnosis Nevertheless, it helps diagnostic thinking to become more methodical, systematic, comprehensive, and demonstrative Although the instrument will greatly assist and potentiate the user's reasoning, it is not a substitute for textbooks, knowledge, experience, clinical acumen, or the ability to take a proper history and examine the patient The possession of uncommon sense and discrimination remains an essential qualification for the diagnostician

In passing, we may note that standard textbooks give the differential diagnosis of each disease However, when one does not know which disease the patient has, one wants the differential diagnostic possibilities of the group of signs and symptoms that particular patient manifests This is obtainable by logoscopy

The mark III rule has a repertoire of over 700 million different combinations, each with its own panorama, showing the patterns of possible cause

The data for programming the strips are compiled from standard textbooks

THE LOGOGRAM

By simple document-copying equipment, one can make a logoscopic record or photogram of the differential diagnostic situation shown on the logoscope at different times during the progress of a case This allows systematic analysis of the changing data at intervals during an illness The logograms can be filed in the patient's casepaper By preparing logograms of typical modes of presentation of each disease one can compare them with other diseases and note and think over differences and resemblances †

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* Generally one s patient may be assumed to be suffering from a condition (or from conditions) in which his symptoms have been described Our first question, therefore, must be ' In what diseases has this combination of manifestations been described? The present logoscope begins and ends here It obtains its extraordinarily powerful narrowing-down effect by considering the possible causes of combinations or conjugations of manifestations On some occasions this mode of narrowing will be sufficient alone When it is not sufficient of itself, either further data must be obtained, or a personal judgment used to differentiate between the possibles ' remaining after the conjugation of manifestations The rule takes no account of the frequency with which a manifestation occurs in a particular disease, nor of the frequency with which a particular disease occurs in a population, nor of the ' importance in diagnosis of a manifestation in a particular disease

† A device, as yet unconstructed, which might be called a contralogoscope would allow side-by-side comparison between diseases In that instrument the removable strips would represent diseases and the category reference index would consist of a list of qualitative and quantitative manifestations

ILLUSTRATIVE CASES

I

A middle-aged man complains of abdominal pain of colicky type and headache, both of some weeks' duration He also complains of recent constipation He has noticed lately that his gums bleed at times The physical examination suggests anæmia, and there is a slow pulse There are no other abnormal findings

Suppose that in this case the physician finds himself unable to make an immediate "recognition diagnosis" How will he proceed? At the moment he does not know whether there is sufficient or insufficient data for a single provisional diagnosis His textbooks show him 94 diseases in which colicky pain can occur, 63 diseases in which constipation has been described, 95 in which headache can occur, 53 conditions in which slow pulse has been described, 85 in which anæmia may occur, and 36 in which bleeding gums have been described He knows that there is probably at least one common factor which he must seek Without an inspired guess, this common factor could only be found by a tabulation, using paper and pencil, but this would take a great deal of his time (He could think his way down the list of causes of bleeding gums, which is the shortest list of the six, having only 36 likely causes, but this is risky because a single symptom may be irrelevant) He wants to know the answer to the question "In what diseases have these signs and symptoms been described?" The logoscope shows that headache, colic, anæmia, bleeding gums, bradycardia, and constipation have been described in no 325, plumbism Further interrogation of the patient reveals that he has spent a lot of time recently cleaning out sludge from aviation petrol tanks This sludge contains lead compounds Confirmation of the diagnosis is made by estimating the lead content of the patient's urine Other investigations are negative Fig 2 shows part of

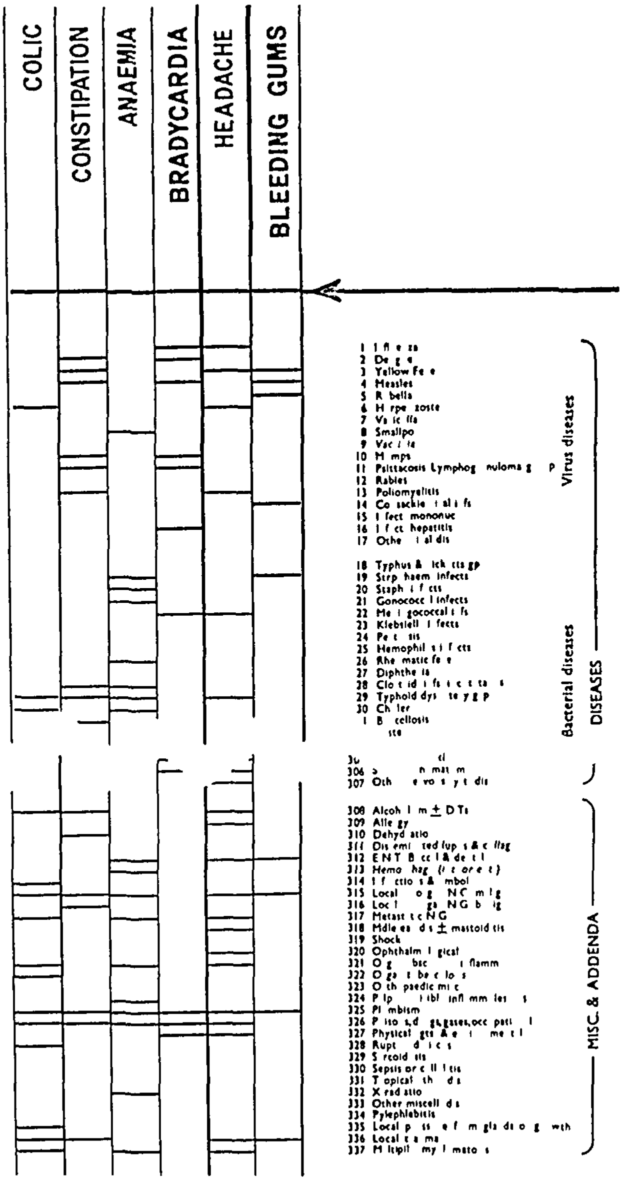

Fig 2—Part of logogram of case of plumbism, showing a complete line against no 325 only

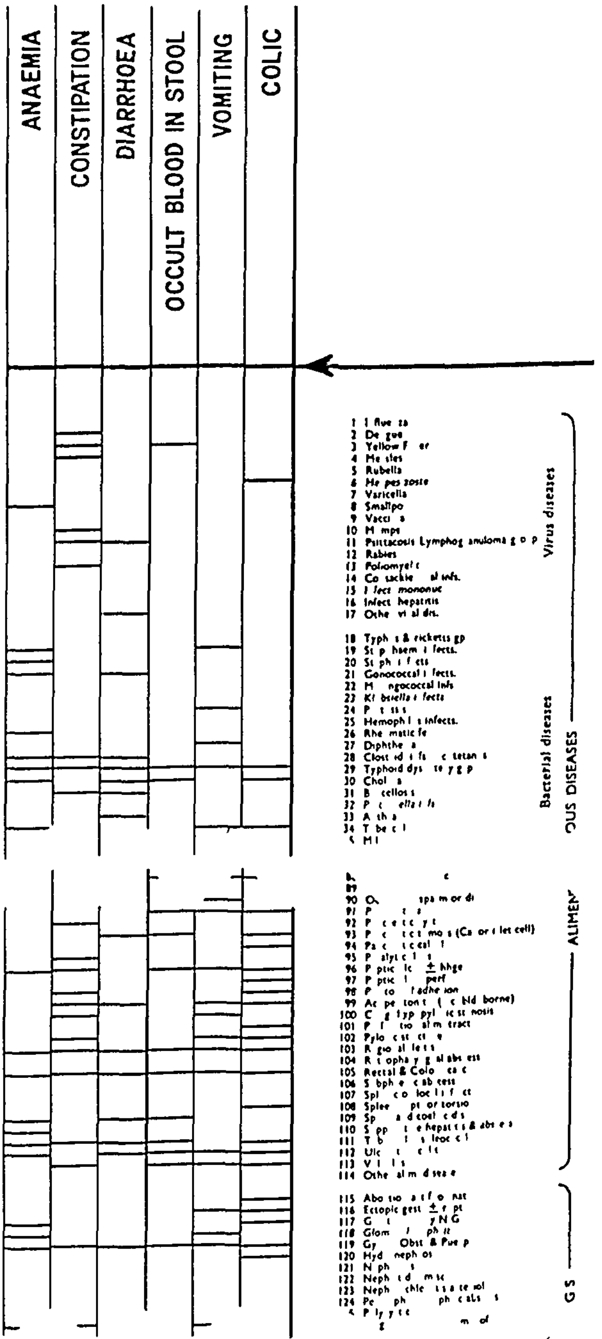

Fig 3—Part of logogram of case of regional ileitis

the logogram of this case There is only one complete line in the whole panorama—against plumbism no 325

It is important to note that in this case the logoscope reveals that there are in fact sufficient grounds for a single diagnosis At other times it will usefully demonstrate that there are insufficient grounds on the face of the information inserted, for a single diagnosis, since the combination of symptoms and signs is compatible with several diseases Although the "primary differentia' shown on the rule may themselves be insufficient to narrow the differential diagnostic field to a single disease the doctor will frequently be able to do this by taking into account the ' secondary differentia "—the other aspects of the case not comprehended by the logoscope Even then, of course, in some cases he will see that he has insufficient grounds for a diagnosis and that he must make further observations

II

Fig 3 shows part of the logogram made of a case from the recent Transatlantic Clinicopathological Conference on gastroenterology (1959) The patient is an 18-year-old girl with a 4 years' history of daily colicky abdominal pain often accompanied by vomiting A year ago, alternating constipation and diarrhoea developed. There is an iron-deficiency anæmia The stools show the presence of occult blood

Thinking our way down the logogram (fig 3) we see that the combination of signs and symptoms has been described in the typhoid dysentery group no 29, but clearly this will not do because the history is too long Farther down we see that there is a complete line across the strips against regional ileitis no 103, and another against no 105—rectal and colonic carcinoma The history is too long for the latter and the patient rather young The primary differentia (those comprehended by the rule) and the secondary differentia (those aspects

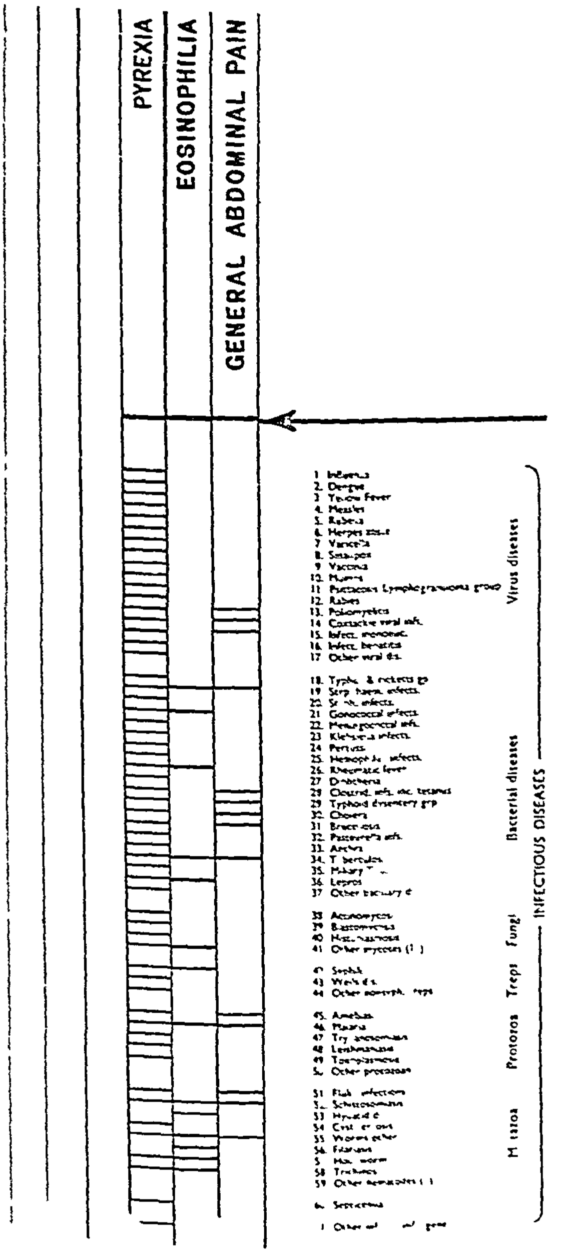

Fig 4—Part of logogram of case of schistosomiasis, on admission

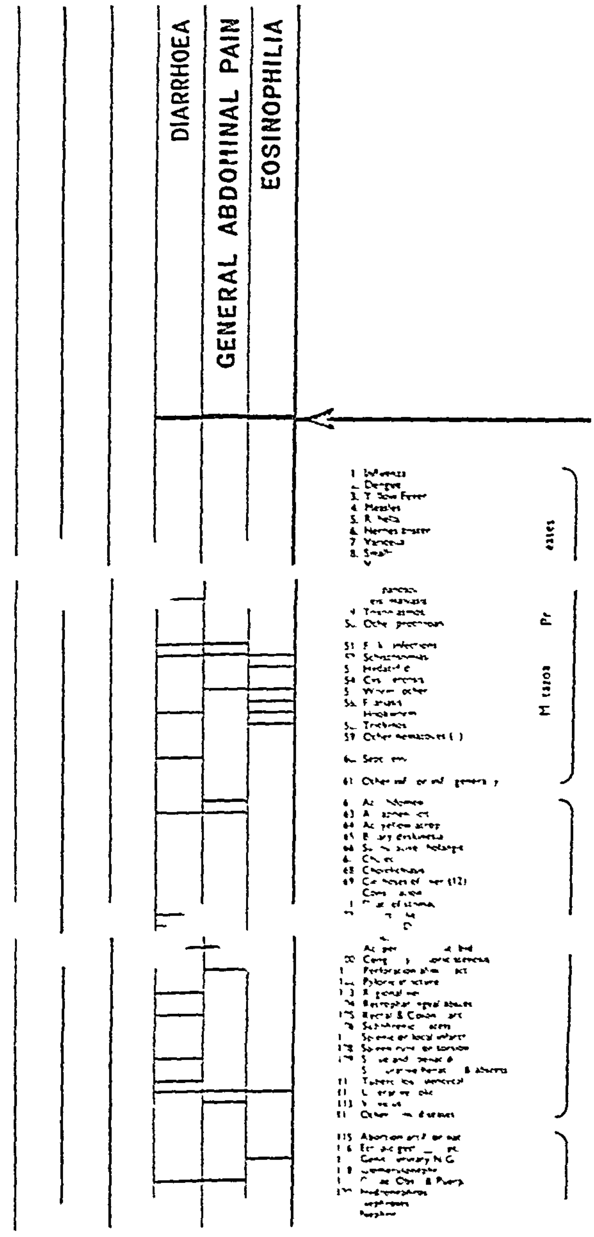

Fig 5—Part of logogram of the same case two weeks after admission

of the case not inserted into the rule) are compatible with the diagnosis of regional ileitis Lower down, at category 119, we see what is called a group-positive under the group title gynæcological, obstetrical, and puerperal This means only that the combination of manifestations has been described in the group of diseases comprehended under this heading It is up to the physician to recall whether there is one disease in the group, which would satisfy the combination of signs and symptoms, or whether they are scattered singly among several diseases included under the group heading

III

Fig 4 shows part of the admission-logogram of a man, aged 35, the main findings being general abdominal pain and fever of apparently a fortnight's duration, and the presence, on admission, of an intense eosinophilia The logogram at this stage shows nine three-line possibilities (five of which are shown in fig 4)

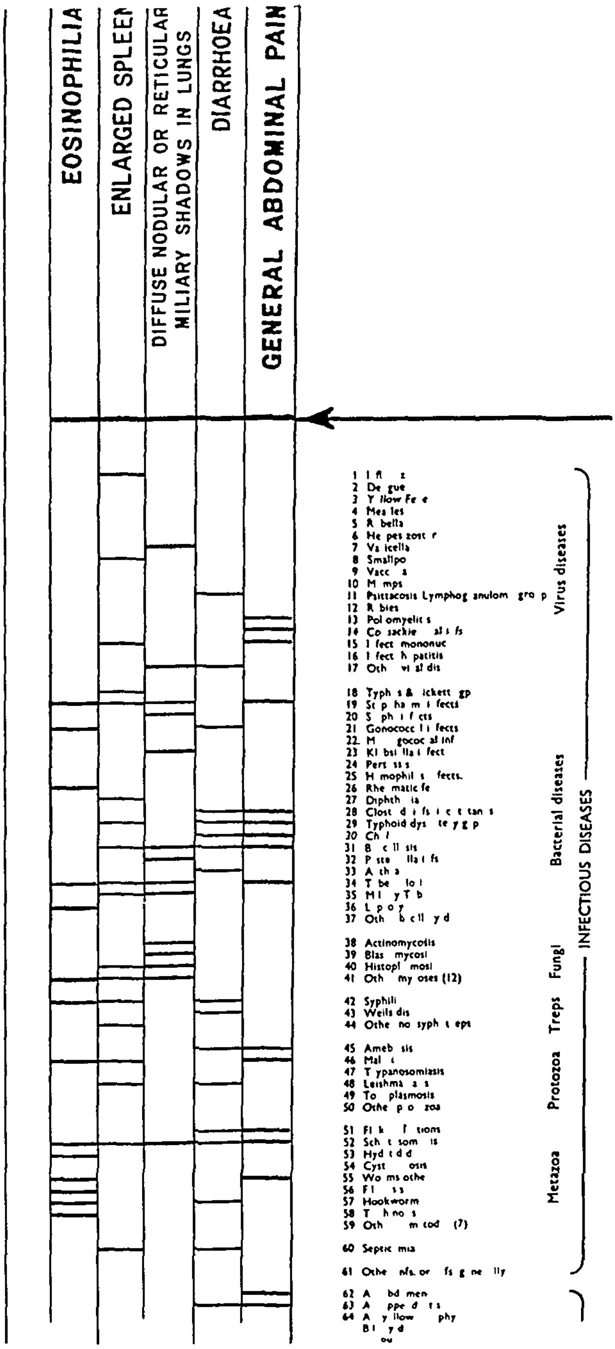

Fig 6—Part of logogram of the same case, four weeks after admission

Fig 5 shows part of a logogram taken two weeks later when the fever has settled, but diarrhœa has appeared The logogram now shows two three-line possibilities—namely, no 52 schistosomiasis and no 112 ulcerative colitis The absence of occult blood in the stool makes colitis unlikely

Fig 6 shows part of a logogram made after a further two weeks—i e, a month after admission New manifestations are enlargement of the spleen and the appearance of fine widespread shadows in the lung-fields On this logogram there is only one five-line possibility—namely, schistosomiasis ‡ By this time, of course, the suspect diagnosis has been confirmed by the recovery of the schistosoma eggs from the fæces of this man who had recently returned from Rhodesia

There is an aspect of diagnosis that may be called classificatory diagnosis This is the allocation of a patient (as a result of enumeration and evaluation of attributes) to a disease A disease is a class containing similar individual cases of illness described by a generalised account In no case will the patient have *all* the described symptoms of any of the textbook diseases, because they are collective descriptions The individual case presents usually but a tattered fragment of the full-blown composite picture of the disease described in the textbook Diagnosis has to be made from *incomplete descriptions* Logoscopy is an aid to classificatory diagnosis, be it nosological, pathological, or physiological, depending on the mode of programming the logoscopes Another aspect of diagnosis, which may be called individual diagnosis, is concerned with the determination of all the individual—i e, unclassifiable—aspects of a case, since it must never be forgotten that each case is, in many aspects, unique These aspects, as well as the shared aspects of illnesses, must, of course, always be taken into account in medical management

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‡ An omission in programming the diarrhœa strip has deprived tuberculosis (no 34) of a complete line The lesson here is—during the think down " be ready to check the programming for omissions Even the collective material from half a dozen textbooks used for programming contains numerous obvious omissions

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" society has made a great invention for the purposes of communication, but it is very rarely used in scientific meetings This invention is conversation I like sometimes to contrast a conversation with a speech In a speech the primary purpose of the speaker is not communication His primary purpose is to hear himself say what he has planned to say in our usual efforts to communicate we tend to give too much attention to our transmitting sets and too little attention to the other fellows' receiving sets "—FRANK FREMONT-SMITH *in* The Central Nervous System and Behavior Transactions of the Third Conference, Josiah Macy, Jr, Foundation, p 17 New York, 1960

In England Now

A Running Commentary by Peripatetic Correspondents

THIS may not be a moral story, but it has a moral My friend the pathologist lives in St Bosolph's Crescent, which is part of a sedate suburb Here is to be found a comforting sameness it is a land of Vauxhalls and Morrises and Fords, no one differing from another by more than a foot in length or £200 in price, and all drawn up in decent line around the Crescent Hitherto, perhaps the most disturbing element in this little community has been my friend himself, for he is a record (Amer disc) addict, and he prefers *fort-* to *pian-issimo*

At lunch the other day he revealed that he had " gone stereophonic " ' You should hear the Brandenburg," he said, "you sit there surrounded by a sea of sound " And so, I suggested, did the neighbours Not a bit of it, he replied, for the house on one side was occupied by an elderly deaf couple, and that on the other side by two hospitable young ladies who weren't all that quiet themselves But soon he might have less accommodating neighbours on that side, for, if the St Bosolph's Residents' Association had its way, the young ladies would be evicted. No, it wasn't the noise or anything like that indeed, they were for the most part model residents, pleasant and companionable, with a ready word for all who cared to pass the time of day The real trouble was the Cadillacs These young women's visitors drove nothing less than a Cadillac or its equivalent, and the sight most mornings of one of these monsters outside the house had deeply disturbed the status sense of the owners of the Vauxhalls, the Morrises, and the Fords, and had roused the S B R.A

Now my friend holds that, however justified the Association's attempted action, it is being undertaken for a base reason, and he has found a neat way of dissociating himself from it It happens that quite often one of these young ladies drives her own car (to be seen at other times in the West End) past the station as my friend emerges to trudge home in the evening For some time past, friendly soul that she is, she has stopped her car whenever she has spotted him, to offer a lift Night after night he has refused, and night after night, cheerfully unsnubbed, the young lady has renewed her offer Now that the S B R.A. has swung into action, the car bowls round the crescent most evenings and discharges two passengers—the young lady, who enters her house, and my friend who, briefcase in hand, enters his

My friend is unperturbed by the possibility of counter-action from the S.B R.A , but I have an uneasy feeling that before long two adjacent houses may be to let in St Bosolph's Crescent.

* * *

For a generation now I have been consulted by students anxious to know how best to plan the defeat of the examiners at the end of the year I have never known what general advice to give them, for in my ignorance I believed that every man is an individual, and must adopt individual methods in order to succeed. But a friend of mine who is taking a degree in education has provided me with the solution which was solemnly laid down for him by his mentors " Organise your knowledge at the recall level " I have been telling this slogan to all my students this year, with the offer of a small prize to anybody who can tell me what the advice means, and a further prize to those who can tell me how to follow it.

* * *

We were rather busy at the time when Dick, our junior partner, had his two top premolars out on one side and an eyetooth on the other Young Rogerson fixed him up with a plate the same day, but the thing did not fit too well when his gums started to shrink. Anyway, he could not get used to doing without the full flavour of bacon and eggs on his hard palate, and the pips from the raspberry jam were a confounded nuisance. The denture spent most of its time in Dick's pocket. Maybe he whistled a bit without it, but middle age brings the first of life's compensations with the same high-tone deafness that makes television more bearable He kept meaning to go back to Rogerson's surgery to get the plate adjusted, but, as I said, the practice was rather busy just then He stuck the thing in for cosmetic effect whenever he remembered, and whipped it out at meal-times It had a little red box when it first came, but the two were seldom together Dick was far too busy to bother with boxes He was working his way unimpeded through a glutinous steak-and-kidney pudding last night when the telephone rang It was Mrs Primslade going into labour with her first so off Dick went to do his stuff

The Primslades were known to be a sticky lot they should have been private patients You know the sort Marcia Primslade had emotions as taut as her perineum There was nothing to do but wait until they both relaxed Dick ran his stethoscope over her heart more to fill in time than anything else The fragrance of talcum powder was tickling his nose he pulled out his handkerchief and stifled a sneeze, without anyone to say bless him, and then retired to sit down on the stool by the dressing-table His eye fell on the triple mirror three Marcias were lifting some objects from their bosoms, poking six thumbs into three mouths in a very strange way He turned back to the bed There was no doubt about it Mrs Primslade was wrestling desperately to get her top dentures in Dick felt a wave of sympathy he walked over to the mantelpiece to gaze tactfully at something safe But next to the French clock was a glass tumbler, half full of water, with a small upper denture in it He felt round his mouth with his tongue, he felt round the gap in his teeth, he felt round the handkerchief in his trouser pocket The truth was only too obvious Marcia was in tears Dick carried the tumbler to the bedside, and without another word the exchange was made Mrs Primslade was delivered in silence We have one less family on our partnership list

* * *

When the chief said we were to get blood-alcohols on every patient who had been involved, however, innocently, in a road accident, I thought it was an interesting idea, but I lost some of my enthusiasm, and some of my faith in our lab's dexterity in the estimation of blood-alcohol when the highest level we got was from an eminently sober Nonconformist minister who was knocked off his bicycle on his way from one chapel to another I was quite alarmed at the thought that some legal issue might depend on one of our blood-alcohol levels when one man whose permission I asked to draw blood for the estimation said, " Sure, take it and let me know the answer If there's none there, I'll sue the pub '

* * *

STANZAS ON SATISFACTORY STOMATA

Oft, when in reflective mood, I muse
Upon the freakish destiny that leads a man to choose
To spend his life (so transient, upon a world so wide)
Thus poised, retractor-laden, by a sleeping patient's side
And often while I meditate, there complements my dreams
The soft and quiet confluence of unobstructed streams

Or e'er the duodenum, with its ravelled loops unloosed,
Is quite reknit, my reveries come home to roost
And thoughts, aforetime lost and straying far afield,
Are sweetly brought cessation as my sober masters wield
The needle—for I know that soon those seams
Will guard the quiet confluence of unobstructed streams

And sure, there is contentment for a surgeon city-bred
(Who carries ever fantasies of rural England in his head)
To see on every working-day enacted all afresh
The garden-makers' miracle—but not in soil, in flesh—
Where little ducts are rivulets and the duodenum seems
A place of quiet confluence of unobstructed streams

And so my mind is easy and my features bear a smile
When folk discuss the gastric juice, the mucus and the bile,
The pancreatic ferments and the pepsin and the acid—
Their complaisant intermixture seems so intimate and placid
That I love this fertile union of unpromising extremes,
This confluence, this Commonwealth of unobstructed streams

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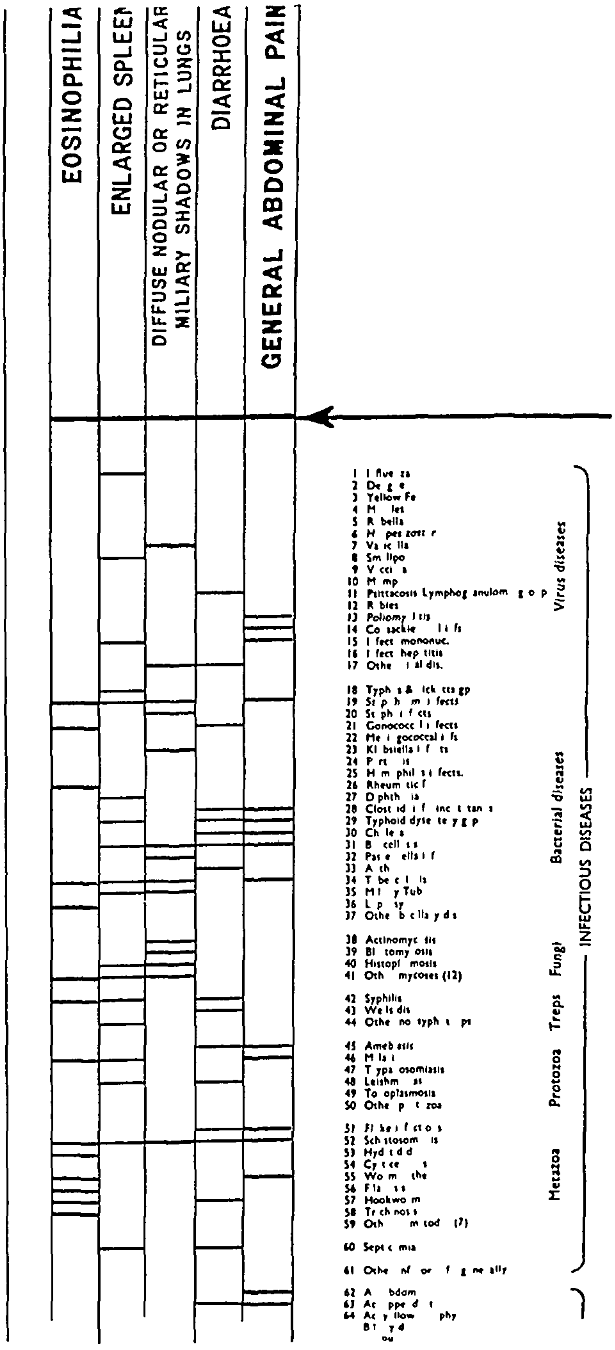

Fig 6—Part of logogram of the same case, four weeks after admission

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Transatlantic Clinicopathological Conference *Brit med J* 1959, ii, 949

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‡ An omission in programming the diarrhœa strip has deprived tuberculosis (no 34) of a complete line The lesson here is—during the think down be ready to check the programming for omissions Even the collective material from half a dozen textbooks used for programming contains numerous obvious omissions

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" society has made a great invention for the purposes of communication, but it is very rarely used in scientific meetings This invention is conversation I like sometimes to contrast a conversation with a speech In a speech the primary purpose of the speaker is not communication His primary purpose is to hear himself say what he has planned to say in our usual efforts to communicate we tend to give too much attention to our transmitting sets and too little attention to the other fellows' receiving sets "—FRANK FREMONT-SMITH *in* The Central Nervous System and Behavior Transactions of the Third Conference, Josiah Macy, Jr, Foundation, p 17 New York, 1960

200 µg per g Ca the release of 70 µg of strontium must be accompanied by 350 mg Ca and 175 mg P This 100 µg of strontium is then eliminated partly by the renal cycle of filtration and reabsorption and partly by the intestine where a similar process of filtration and reabsorption may be postulated If strontium entered the upper intestine with calcium by ultrafiltration, a process of reabsorption with preferential selection of calcium could lead to the observed enrichment of strontium in the final fæcal discharge Many species of animals, notably ruminants, discharge their alkaline earths by the gut rather than the kidney, and experimental studies in rats indicate that labelled strontium enters the gut, particularly the jejunum, from the plasma What has to be acceptable is the tremendous throughput of fluid both ways across the gut wall Thus the minimal figures suggest in the human infant a dietary intake of some 400 ml per day and a recycling of 4000 ml across the gut wall If the process is not limited to breast-fed infants and the same assumptions are made for bottle-fed, the following figures emerge

	Breast fed			*Bottle fed* (*a*)			*Bottle fed* (*b*)		
	Sr (µg)	Ca (mg)	P (mg)	Sr (µg)	Ca (mg)	P (mg)	Sr (µg)	Ca (mg)	P (mg)
In									
Diet (*a*)	28	124	67 5	122	470	360	252	470	360
Recycled* (*b*)	56	280	140	56	280	140	56	280	140
Total (*a*)+(*b*)	84	404	207 5	178	750	500	308	750	500
Out									
Fæces (*c*)	49	54	7 5	84	185	61	66	185	61
Net absorbed (*a*)+(*b*)−(*c*)	35	350	200	94	565	439	242	565	439
$\frac{\text{Sr/Ca absorbed } (a+b-c)}{\text{Sr/Ca } (a+b)}$	$\frac{0\ 10\times10^{-3}}{0\ 21\times10^{-3}}\simeq0\ 5$			$\frac{0\ 17\times10^{-3}}{0\ 24\times10^{-3}}\simeq0\ 7$			$\frac{0\ 43\times10^{-3}}{0\ 41\times10^{-3}}\simeq1$		
$\frac{\text{Ca/P absorbed } (a+b-c)}{\text{CaP } (a+b)}$	$\frac{1\ 75}{1\ 9}=0\ 9$			$\frac{1\ 3}{1\ 5}=0\ 87$			$\frac{1\ 3}{1\ 6}=0\ 87$		

* 4000 ml at 7 mg Ca, 1 4 µg, Sr, 3 5 mg P per 100 ml

It would seem that the maximum discrimination in intestinal absorption of the breast-fed infant is about twofold It may be less in the bottle-fed but, as there is no lack of phosphate with this nurture, calcium-phosphate turnover may not be as large as postulated However, low values of discrimination for the immature have been demonstrated by Comar [2] in calves

This extraordinary phenomenon of the breast-fed infant's burgling its bones for their phosphate, it would seem, still allows growth and a positive calcium balance Thus the reforming bone mineral should be depleted not only in strontium but in phosphate and presumably therefore rich in other anions Presumably such behaviour is made possible only by the uniqueness of the infant's potential in bone-turnover

Medical Research
Council Radiobiological
Research Unit,
Harwell Berks

JOHN F LOUTIT

MUTATIONS AND SEX-LINKED THROMBOCYTOPENIA

SIR,—Our investigations of a patient with the Aldrich syndrome coincided with the publication of your annotation [3] on this fascinating disease

Our patient, an 8-year-old Jewish boy, has had severe thrombocytopenia (20,000 platelets per c mm) since birth He has had moderately severe eczematoid dermatitis, severe asthma, and frequent episodes of pneumonia as well as staphylococcal skin infections He has one normal older sister The father has hay-fever but is otherwise normal, as is the mother and her only brother A careful search of the pedigree in both parents, with special reference to maternal relatives, failed to reveal any instances of early death due to bleeding or infection

Your annotation insists on the importance of a positive family history in this syndrome All cases compiled by Gordon [4] died during childhood The disease, therefore, may be considered as genetically lethal The population frequency of a lethal sex-linked recessive disease is determined by the balance established by gene loss due to death of affected males and new mutations With complete lethality, one-third of all male cases of a sex-linked recessive lethal condition should be due to new mutations and therefore be truly sporadic A further third of cases on the average will be due to mutations in the X chromosomes of either grandparent If the mutant daughter has only few sons, as in our case, a " pseudosporadic " case can easily result From these considerations one would expect that approximately 50% of all cases with the Aldrich syndrome would *not* give a positive family history

The separation of sporadic from pseudosporadic cases is important for genetic prognosis, since patient's sisters cannot be carriers in truly sporadic cases while their chance of being carriers will still be 50% in the pseudosporadic cases In the absence of laboratory techniques for carrier detection, one must therefore keep in mind that sisters of isolated cases may pass on the disease

May I call attention to a report by Wiskott,[5] who described three brothers with thrombocytopenic hæmorrhage, lack of resistance to infection, and eczema Death occurred at 18 months, 4 months, and 8 months Four sisters were normal, as were the parents and an unstated number of ancestors Presumably this report represents the first account of this unusual condition

University of Washington,
Seattle, Washington

ARNO G MOTULSKY

GONADAL DYSGENESIS (TURNER'S SYNDROME) WITH MALE PHENOTYPE AND XO CHROMOSOMAL CONSTITUTION

SIR,—We were interested to read the article by Dr Bloise and others (Nov 12) We will not comment on the aptness of the term " Turner's syndrome " in this situation, but we should like to suggest a possible explanation for the findings in this case, after commenting on the authors' use of the term " male phenotype "

The detailed presentation of this case leaves no doubt about the presence of intersexuality The only feature compatible with a male phenotype is the abnormal testis-like gonad (and, perhaps, the phallus) The position of the gonads, the presence of uterus and tubes, and the complete separation of vagina and perineal urethra are typical of the female The only correct designation of the phenotype, therefore, is " intersex "

In view of our recent publication of a case of true hermaphroditism with mosaicism of the XY/XO type,[6 7] as well as the description of two similar adult patients with XY/XO mosaicism by one of us,[8] we suggest that if skin and peripheral blood are studied, evidence for such mosaicism may be found in this individual, most of whose anatomical abnormalities were quite similar to those found in the three cases we have studied Two of our cases were true hermaphrodites, one of whom had almost no ovarian tissue but abundant testicular tissue The third case had few seminiferous tubules in streak gonads and could be considered as a variant of Turner's syndrome or of true hermaphroditism

A reinterpretation of the results found in several other reported cases of true hermaphroditism is necessary if we are to retain confidence in at least one of the impressions gained from recent work on human chromosomes—i e , that a Y chromosome is a prerequisite for the formation of testicular tissue We do not have evidence supporting such a re-interpretation, in fact, one of us (O J M , un-

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[2] Comar C L , Wasserman, R H *in* Progress in Nuclear Energy, Biological Sciences vol 1, p 175 Oxford 1956

[3] *Lancet* Nov 12, 1960, p 1074

[4] Gordon, R R. *Arch Dis Childh* 1960 35 259

[5] *Mschr Kinderheilk* 1937 68 212

[6] Hirschhorn K Decker, W L , Cooper, H L *Lancet* Aug 6 1960 p 319

[7] Hirschhorn K Decker W L , Cooper, H L *New Engl J Med* 1960 263 1044

[8] Miller O J (to be published)

Letters to the Editor

RETIREMENT OF MEDICAL RESEARCH-WORKERS

SIR,—The problem posed by " Aged 60 " (Dec 17) of what medical research-workers can do when they retire obviously affects all experimental research-workers who require more or less elaborate laboratory or hospital facilities as the tools of their trade Few in these days are likely to have accumulated sufficient funds to equip private laboratories An increasing proportion will have worked until retirement for organisations or institutions which have little flexibility (because of their regulations or lack of space) for permitting people to work after reaching retiring-age The more a research-worker's life and interests have been absorbed in his researches, the harder is likely to be the impact of abrupt retirement

The registration scheme proposed by your correspondent might be practicable and helpful Another additional suggestion might be worth considering A proportion of those who have spent a good many years in research are likely to have considerable experience in writing and editing scientific papers, and a reasonable grasp of current work in their own and related fields Might they not be invited to assist in the detailed editorial work of scientific journals, which takes time and effort sometimes grudged by younger colleagues who are still in a position to do bench work? This already happens to a certain extent, but it would not be fair to expect that many newly retired persons should undertake such editorial duties unless they can be paid for doing so Retirement pensions are seldom so generous that some additional earnings are not more than merely welcome Scientific journals, however, are seldom in a position to pay their editors anything more than nominal sums, unless these journals have large circulations The suggestion is that grants for editorial assistance be made to scientific societies which produce journals, and that these be used for part-time or full-time employment of retired persons The annual medical examination proposed by your correspondent would, of course, be necessary Since I have still some twenty years to go I can sign my name in full

London, N W 7 J H HUMPHREY

PREMEDICATION WITH ATROPINE

SIR,—Dr Murphy (Dec 10) expresses the view that for tonsillectomy, especially by the guillotine method, an adequate preoperative dose of atropine by injection is of supreme importance

When tonsillectomy is performed by the guillotine method, I feel there is no need to give any premedication at all, provided anæsthesia is produced by non-irritating inhalational agents and the child is correctly approached Ideal operating conditions can be provided by a combination of nitrous oxide, oxygen, and minimal halothane Induction is rapid, relaxation of the jaw and pharynx is good, anoxia is avoided, the trachea-bronchial tree relaxes, secretions are inhibited, and recovery of active reflexes is rapid without laryngeal spasm or cardiac arrhythmia In this operation, good team-work between anæsthetist, surgeon, and nursing staff is, of course, of prime importance

Department of Anæsthetics,
Royal Infirmary, Aberdeen W N ROLLASON

ABSORPTION, EXCRETION AND RETENTION OF STRONTIUM BY BREAST-FED AND BOTTLE-FED BABIES

SIR,—When such widespread interest has been elicited on the hazards of strontium 90, it is surprising to me that no comment has been forthcoming from this country (except on an error in drafting) or from abroad, about the significance to be attached to the findings of Dr Widdowson and her co-workers reported in your issue of Oct 29 They themselves identified the important role of an adequate intake of phosphate in determining the retention of strontium by the newborn In the past others have concentrated on the relative distributions of strontium and calcium In this connection much could be deduced from the data given in this paper

Mammals, man and experimental animals, do discriminate in some physiological processes between calcium and strontium—notably when the two ions pass across cellular barriers, possibly by active transport In all instances so far the data are to be interpreted that calcium passes more freely than strontium Thus in absorption from the gut, secretion by the mammary gland, and passage across the placenta, calcium is favoured Strontium is excreted preferentially by the kidney, but the interpretation in this case is selective tubular reabsorption of calcium from the glomerular ultra-filtrate

The overall discrimination under equilibrium conditions between diet and deposit in bone is mainly a product of alimentary and renal discriminations

Widdowson et al in their table II give the following mean figures for intake, urine, and fæces of the breast-fed and two groups of bottle-fed babies

Group	*Intake/day*		*Excretion/day*			
			Urine		*Fæces*	
	Sr (µg)	Ca (mg)	Sr (µg)	Ca (mg)	Sr (µg)	Ca (mg)
Breast fed	8	35 7	14	5 3	14	15 4
Bottle fed I	35	135	2	2 4	24	52 8
Bottle fed II	72		2		19	

None can be considered to be in a state of equilibrium, they are in fact in a state of transition and the breast-fed infants are in negative balance for strontium though positive for calcium Nevertheless, it is not unfair to look at individual physiological processes in a speculative fashion

Renal discrimination —It is important to know whether the immature kidney of the infant can discriminate in the same qualitative fashion as the adult's Although data on the values of strontium and calcium in plasma were not given the ratio Sr/Ca should not have been far removed from 0 2 mg Sr per g Ca since the average value in bone of the newborn, which is in equilibrium with plasma, is about $0\ 2\times10^{-3}$ according to numerous analyses by Bryant et al [1] The ratios

$$\frac{\text{Sr/Ca urine}}{\text{Sr/Ca plasma}}$$

therefore range from about 13 to 4 According to the simplest model of glomerular filtration and tubular reabsorption this indicates substantial discrimination in the infant's kidney

Intestinal discrimination —The usual formula for evaluating this phenomenon is

$$\frac{\text{Sr/Ca absorbed}}{\text{Sr/Ca diet}} = \frac{\text{Ingested Sr—Fæcal Sr}}{\text{Ingested Ca—Fæcal Ca}} \Big/ \frac{\text{Ingested Sr}}{\text{Ingested Ca}}$$

but the application of this would, because of the disequilibrium, give negative values for breast-fed infants and 0 5 and 1 2 for the two bottle-fed groups

To explain this Widdowson et al invoke secretion of strontium by the intestine, but preferential secretion of strontium relative to calcium would be against discriminatory behaviour as we know it so far

To account for the total excretion of some 100 µg of strontium per day from a standard breast-fed infant of 3 5 kg, one must, taking the limiting case, assume that all of the 28 µg dietary strontium is absorbed and some 70 µg of strontium mobilised from the bone From bone with a concentration of dystonic-dyskinetic syndrome is temporarily under the control of the will, it is also symptomatically relieved by barbiturates for a while, and effectively controlled by antiparkinsonian agents such as orphenadrine, the drug which at our present stage of inquiry we prefer Antihistaminics, with but slender antiparkinsonian activity, are of less value

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[1] Bryant, F J Personal communication See M R C Monitoring Report Series no 1 H M Stationery Office, 1960

(4) Dr Barker and Dr Kerr have thrown up many interesting talking-points, but as the tolerance limits of the casualty-officers with whom we are concerned must be fast approaching we will conclude with a few brief points akathisia or dejected apathetic inertia, may immediately antecede dystonia-dyskinesia if a history can be got, the dystonic-dyskinetic, because of his peculiar psychic state, is less distressed than the casualty-officer, the patient looks more ill than he is, "spasm of the glottis" has not been reported, nor heard of by any of us in personal communications, many phenothiazines have an adrenaline-reversal effect, the patient is likely to escape from his predicament by the simple expedient of swallowing an orphenadrine tablet

Herrison Hospital
Dorchester

R H BOARDMAN
ALEX FULLERTON
MAX BETHELL
STELLA CONWAY

PULMONARY HYPERTENSION

SIR,—If I say to Dr Pappworth (Dec 17) "censorious", he will hear in less than a second many more than five sounds, and with practice he could report on them individually If I say to him "Llaellw" he may not be able to identify as many Similarly he may, like many of us, find the language of the heart difficult or think it nonsensical, but he cannot reasonably object that the number of signals per second is too high for the ear of the expert

This is not of course to deny the importance of that insistence on the fundamental which Dr Pappworth shares with the censors of the Royal College of Physicians to the great benefit of many

Oxford.

T H HUGHES-DAVIES

SIR,—Why should Dr Pappworth be so incredulous? Most watches tick at 5 per second and most people can distinguish the five ticks without any difficulty

Surely the best test of a doctor's ability to hear and identify heart-sounds correctly is to compare his opinion with an appropriate phonocardiogram, not by his ability to pass the M.R C P But if this *is* a test that satisfies Dr Pappworth, he should accept the opinion of Dr J F Goodwin, F.R C P

Richmond Green,
Surrey

C M FLETCHER

UNUSUAL REACTION TO OXYTETRACYCLINE

SIR,—During the administration of oxytetracycline we observed the following peculiar reaction

One of us (K G) was admitted to hospital with coronary thrombosis and treated with heparin, nicoumalone ('Sintrom', 'Syncumar'), penicillin, and streptomycin for 8 days On the 12th day pleurocardial friction developed, with severe pain behind the sternum Temperature 37 6°C (99 5°F), pulse-rate 88, blood-pressure 120/80 mm Hg Acute pericarditis was diagnosed and oxygen was given through a thin nasal catheter The patient was given an intravenous drip infusion of oxytetracycline (terramycin) (500 mg in 500 ml physiological saline) The solution was crystal clear and golden yellow After the first few drops a slightly bitter taste was apparent at the sides of the root of the tongue, and soon the patient became pale, sweated profusely, and had bradycardia, arrhythmia, and psychomotor restlessness The pulse became impalpable The infusion was promptly stopped but the patient felt suffocated After more oxygen was given he slowly recovered The episode lasted about 10 minutes

Intravenous infusion of the same drug in other patients had no such effect

The bitter taste might serve as a signal that a similar reaction was imminent

Budapest.

K GEFFERTH
Z PAP

"THEY NEVER TELL YOU ANYTHING"

SIR,—I write to commiserate with Mr Windo (Dec 17) in his rotten luck in encountering the only ward sister in the kingdom with insufficient "responsibility to impart some kind of information" about sick relatives In his own hospital by night and day, he will often have seen these splendid women talking, with kindness and tact, to relatives about their loved ones

I am glad to learn that the thoughtful tradition of the medical staff being employed elsewhere than the wards during visiting-hours persists in the hospital in question

Only a very little initiative is necessary to loosen the gossamer "shackles of silence" Were any of the following simple measures used?

(1) Was the ward-sister asked to arrange an appointment with one of the resident staff during the visit? They work quite long hours and are available at all hours of the day and night, and at all weekends

(2) Was the consultant, registrar, or houseman in charge asked for information by telephone or letter?

(3) Was the patient's own general practitioner contacted? If he did not know the full facts, I am sure he would have most willingly found out

Aldeburgh,
Suffolk

JOHN STEVENS

SIR,—I cannot allow Mr Windo's letter to pass without comment

My mother, also aged 80, underwent a major operation three weeks ago A few days after the operation I took the trouble to find out when the consultant surgeon would be available, and I saw him the next day after his ward round He kindly gave up a quarter of an hour of his time to give me the full details of my mother's condition including ætiology, diagnosis, treatment, and (within limits) prognosis, though like Mr Windo I am a layman

Nobody could have been more courteous or helpful and on other occasions when I visited the hospital I frequently saw the house-surgeon who was always informative and friendly

It takes all sorts to make a world

London W C 1

F M STENT

NEW IDEAS ON EPIDEMIC VIRUS INFECTIONS

SIR,—If you care to refer to your issue of Nov 18, 1922, I think you will agree that to one student, so far as the virus of influenza is concerned, the observations reported in your leading article of Nov 19 should have been neither surprising nor unexpected

You devoted a column to an annotation on Unorthodox Views on Influenza summarising an article of mine in the *Glasgow Medical Journal* of October, 1922 The annotation is headed by a quotation from the advice given by the Ministry of Health in its report on the pandemic of 1918

> At the first feeling of illness, or rise of temperature, it is the private and public duty of the patient to go to bed at once, to remain at rest and in warmth

Looking back I do not think that the advice led to any great increase in the death-rate it was based on that of the Royal College of Physicians and was simply voicing popular beliefs, personal inclination, and the usual practice of the profession In my own neighbourhood I knew of the death of one patient who had called in another doctor I saw to it that the windows published) has also found a typical female karyotype in three chromatin-positive true hermaphrodites Nevertheless, it is possible, and from our viewpoint probable, that some of these patients will exhibit XXY/XX mosaicism when more than one tissue is studied We do not, of course, mean to imply that abnormal chromosome numbers, or other chromosomal abnormalities, can account for all the abnormalities of sex differentiation

Department of Medicine,
New York University
Medical Center
KURT HIRSCHHORN
HERBERT L COOPER

Department of Obstetrics
and Gynecology
Columbia University College of
Physicians and Surgeons
ORLANDO J MILLER

CHROMOSOMES IN THE STURGE-WEBER SYNDROME

SIR,—Mr Hayward and Dr Bower (Oct 15) described trisomy in the 22nd pair of chromosomes in a case of the Sturge-Weber syndrome, and we therefore examined cytogenetically two patients with this syndrome, a girl of 17 and a young man of 18 Both had earlier been thoroughly investigated clinically

We studied the chromosomes of leucocytes from circulating blood, using a slight modification of the technique described by Hungerford et al [1] In the first case we got a large number of mitoses of good quality, which permitted chromosome counting and thorough pairing In the second case we got 5 mitoses which allowed counting only In both cases the number of chromosomes was 46 and in the first case the idiogram was normal

Thus, though trisomy of no 22 has been reported in the Sturge-Weber syndrome, apparently it is not always present This is as you surmised in your leading article of Nov 12

Pediatric Department and Institutes of
Histology and Social Medicine,
University of Gothenburg
Sweden
O LEHMANN
H FORSSMAN

EXAMPLE OF XY/XO MOSAICISM

SIR,—Hirschhorn and his colleagues [2] briefly described their findings in a case of true hermaphroditism The patient was a three-month-old infant with a phallus, vagina, hypospadias, and an ovotestis Analysis of the chromosome complement of cells grown from bone-marrow indicated XY/XO mosaicism

We should like to report a second example of presumed XY/XO mosaicism

A 55-year-old “ woman ” presented with a psychosomatic disorder of the left upper limb A history of primary amenorrhœa stimulated investigation of sex-chromatin state and karyotype

She seemed to be well below average intelligence She was short, rather plump, and had a short neck Her breasts were poorly developed, her chest broad, and her hips narrow A right paramedian scar was present on her lower abdomen Axillary and pubic hair were present and of female distribution The external genitalia were of female type The clitoris was fairly long but the vaginal introitus was small A small cervix could be felt rectally

Well-defined sex-chromatin bodies could not be detected in buccal mucosa preparations No nuclear appendages of female type were noted in 510 polymorphonuclear leucocytes examined Leucocytes derived from peripheral blood were cultured for three days and prepared for chromosome analysis The chromosomes in 100 suitable cells were counted 58 cells contained 46 chromosomes and 41 contained 45 chromosomes In 20 cells, 10 with 46 chromosomes and 10 with 45 chromosomes, the chromosomes were analysed in detail In each of the 10 cells containing 46 chromosomes 5 small acrocentric chromosomes were present and the chromosome complement was not demonstrably different from that observed in normal males In each of the cells containing 45 chromosomes only 4 small acrocentrics were noted The acrocentric missing from the cell with 45 chromosomes is presumed to be the Y chromosome and the patient an XY/XO mosaic

Thirty-three years ago a laparotomy was performed to determine the cause of persistent lower abdominal pain At that time it was noted that there was evidence of chronic pelvic inflammation, of uncertain ætiology, a very small uterus and a small ovary on the left side No gonad could be identified on the right side Sections of the left gonad were not taken

A more complete description of the findings in this patient will be reported later

The research reported here is part of a programme supported by a grant from the Medical Research Council

Department of Genetics,
University of Sheffield,
and Royal Infirmary,
Sheffield
C E BLANK
AUDREY BISHOP
J P CALEY

MUSSEL POISONING

SIR,—Dr Gemmill and Dr Manderson described a case of mussel poisoning in your issue of Aug 6

We ourselves process mussels and finally vacuum-pack in jars containing a 4% spirit vinegar solution, and we are naturally anxious to know whether the bacteria concerned can survive the processing of cooking for 10 minutes at 180°F and final packaging in spirit vinegar

J E BOZMAN
Hull
Director, Maconochie Kippers Ltd

OVERDOSE OF TRIFLUOPERAZINE

SIR,—The letter by Dr Barker and Dr Kerr (Dec 10) illustrates how tragically the sub-disciplines within the discipline of medicine are diverging as specialisation necessarily develops

The extrapyramidal phenothiazine syndrome, which evidently appears as a devastating experience to a casualty-officer, is part of the bread-and-butter of a psychiatric nurse

In view of the effort in their letter to enlighten casualty-officers who may meet this condition, there are a few observations of our own which we feel we could profitably add

(1) Unequivocal extrapyramidal signs can arise with a trifluoperazine intake as low as 6 mg a day, and a dystonic-dyskinetic syndrome at least as well developed as that described may be seen on a dosage of 20 mg a day This presentation is therefore not necessarily a prelude to death

(2) It does not seem to us that death was possible with a dose of 140 mg In acute experiments in rats, trifluoperazine has about a quarter of the toxicity of chlorpromazine, and its oral LD_{50} is 1150 mg per kg [1] If man is comparable, the LD_{50} of a 10-stone specimen would be of the order of *70,000 mg*

Rudy et al speaking of man, said “ dosage did not exceed 30 mgm 4 times a day ”, and do not imply that at 120 mg a day, in a chronic study with a cumulative drug, they are approaching toxic levels

(3) Caffeine benzoate was formerly advocated by Freyhan [3] to counter extrapyramidal symptoms, but has not been generally used for at least two years, having been superseded by other agents

As Dr Barker and Dr Kerr so pertinently observe, the

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[1] Hungerford, D A , Donnelly, A J , Nowell, P C , Beck, S *Amer J hum Genet* 1959 **11,** 215

[2] Hirschhorn, K , Decker, W H , Cooper H L *Lancet*, Aug 6, 1960, p 319

[1] Tedeschi D H , Spencer J N , Macko, F , Tedeschi, R E , Leonard, C A , McLean, R A , Flanagan, T , Cook, L , Mattis P A , Fellows, E J *in* Trifluoperazine p 29 *Philadelphia* 1958

[2] Rudy L H , Himwich, H E , Costa, E , Rinaldi, F *ibid* p 169

[3] Freyhan, F A *ibid* p 203

At the hearing before the Disciplinary Committee he had argued that the need existed for an authoritative book on cosmetic surgery, and he wished to adduce in evidence p 392 of the *British Medical Journal* of Aug 6, 1955, to show the attitude of the B M A to this branch of surgery He also wished to base one of his grounds of appeal on the fact that the decision to erase his name was unreasonable It was very strange, concluded Dr Gardiner, that he should be the only doctor who had been found to have advertised by writing a book.

Mr PETER BOYDELL, who appeared for the General Medical Council, said that Dr Gardiner had not shown that the new evidence was not available at the hearing before the Disciplinary Committee or that it would have had, or been likely to have had, a determining influence on the decision The proposed evidence went solely to the standard to be applied by the Disciplinary Committee

Lord TUCKER, after consultation, adjourned the petition to be dealt with by the Board on the hearing of the appeal.

Gardiner v General Medical Council—*Judicial Committee of the Privy Council* Lord Tucker, Lord Denning Lord Morris of Borth y Gest Dec 19, 1960 Counsel and Solicitors The petitioner in person (Henry Solomon & Co), Peter Boydell (Waterhouse & Co)

CHARLES CLAYTON
Barrister at-Law

Non-communication Widow's Appeal Dismissed

A butcher was boning a rump of beef when the knife slipped and caused a wound in his abdomen

A telephone call for a doctor and ambulance was sent to a cottage hospital with no resident medical staff A general practitioner, Dr R, happened to be there when the message came and at once arranged for a bed to be held at a nearby general hospital He then went to the man's place of work, made a quick examination of the wound, and had him sent to the cottage hospital where he examined the wound more carefully He concluded, wrongly as it proved, that though the deep fascia had been cut the wound had not penetrated the peritoneum, accordingly he had the wound stitched up and sent the man home, telling him that he thought it was only a surface wound, but giving him emphatic instructions to see his own doctor that evening and tell his doctor what had happened and what had been done Dr R then cancelled the bed at the general hospital

When the man's own doctor, Dr M, called that evening, abdominal pain and nausea had developed The man told Dr M that the "hospital" had said that the wound was 'superficial", but Dr M, not appreciating that the hospital was a cottage hospital or the status and role of Dr R, examined his patient and diagnosed a digestive disorder During the next 36 hours the man's condition deteriorated and he died in hospital after operation A postmortem examination disclosed that the wound had penetrated the small intestine

The widow brought proceedings for negligence against Dr R on the ground, inter alia, of failure to send a written message to or otherwise communicate directly with Dr M to report the history of the accident, the condition of the deceased, and the steps taken to investigate the extent and nature of the injury or to warn him of the possibility that the wound had penetrated to the abdominal cavity The trial judge held Dr R negligent on that ground only, namely, failure to communicate with Dr M directly by telephone or letter, and he awarded the widow £9050 damages[1] The Court of Appeal, by a majority, allowed the doctor's appeal[2] The widow appealed to the House of Lords

The House, Lord KEITH and Lord DENNING dissenting, dismissed the appeal

Lord KEITH OF AVONHOLM said that the patient fell between two stools due chiefly to failure of communication

Some communication from Dr R to Dr M was essential There was some communication, and the patient himself was made the medium of that communication The question was Was that communication adequate and if not was Dr R responsible for the inadequacy and did his failure amount to negligence ? In his Lordship's view Dr R should have foreseen that the patient's doctor, whoever he was, not having all the information that he, Dr R had, might not act as Dr R himself would have acted, and indeed that the message which he sent would tend to mislead rather than otherwise That it did tend to mislead Dr M was clear from his evidence of how he treated the patient on the night in question A doctor who was expected to look after a patient with an abdominal wound, which had already been diagnosed and treated by another doctor who had decided that the injury did not require operative or observational treatment in a hospital, should be put in possession of information as to what had been observed and done by the first doctor Otherwise the patient was deprived of the full skill, knowledge, and aid in diagnosis that the second doctor could apply to his case

His Lordship hardly regarded this as a medical question at all In his view this non-communication amounted to negligence in law, and it was scarcely in the category of professional negligence Dr R deserved great credit for the steps he took to deal with this unfortunate case, he did what he thought best in every way for the patient But he did not foresee what the results would be of sending the patient home with such an encouraging message What was foreseeable was that the patient's medical adviser would be handicapped by lack of all the information that Dr R himself had obtained The result was the delay in sending him to hospital for operation His Lordship would allow the appeal

Lord GODDARD, dismissing the appeal, said it was clear that in acting as he did Dr R was actuated firstly by his opinion that the wound was superficial but also by his view that it was necessary for the patient to be kept under observation For what other reason had he been so insistent that the patient's own doctor should be called in and advised as to what had happened and had been done ? Their Lordships knew now that unhappily Dr R's diagnosis was wrong, but he had been acquitted of any negligence in forming that diagnosis No doctor was to be held liable for a mistake if he had used the degree of care expected of him and acted in accordance with recognised practice

His Lordship could not see that Dr R in any way misled Dr M If he had written or spoken directly to his fellow practitioner his Lordship doubted whether he would have told him more than that after observation and probing he had formed the opinion that there was no penetration, though he might have added "He needs watching', but that he might well assume Dr M would understand without being told His Lordship was not saying that Dr M must be considered negligent, it would be wrong to do so as he was no party to the action But his Lordship protested against the view that if either of these two gentlemen was not negligent the other must have been The finding of negligence against Dr R should be reversed

But his Lordship could not agree that if in the Court of Appeal Lord Justice Romer had meant to say that if a doctor charged with negligence could find two other doctors to say that they would have acted as he did that of itself entitled him to a verdict, if there was evidence the other way His Lordship preferred to think that what Lord Justice Romer meant was that if there were two recognised schools of thought on a subject one could not be negligent He would dismiss the appeal were kept open, and I heard that the first words of my colleague when he entered the sick-room were " Shut those damned windows "

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[1] See *Lancet* 1958 ii 1118
[2] *ibid* 1959 ii 965

I commented in my article on the difficulties a young man had to face in fighting the advice of such a high authority May I add a postscript, now I am retiring? In the article I reported the case of a well-known young man who had heliotrope cyanosis, red-current-jelly sputum, and was delirious when I first saw him A tarpaulin was spread over his bed to protect it from the sleet and snow blowing in at the opened windows He died in 1954 of a coronary thrombosis A few days after his death a patient recalled the incident and said, " Believe me, doctor, Jack's recovery made you, for the whole of Boothtown was watching "

The observation of the Dutch workers is the probable explanation of my rule in regard to prognosis [1]

Boothtown, Halifax A GARVIE

Medicine and the Law

A Hospital Board's Responsibility

A MAN was knocked down by a lorry in January, 1954, and seriously injured, necessitating his admission to hospital and an operation for surgical toilet later the same day

He was anæsthetised with an explosive mixture of oxygen, nitrous oxide, and cyclopropane While he was on the operating-table it became necessary to deepen anæsthesia, and the anæsthetist decided to change from an open to a closed anæsthetic circuit For this purpose he had to remove the terminal metal cylinder of the breathing-tube from a metal orifice on the anæsthetics trolley As he did so a spark, caused by a static electrical charge on the apparatus, ignited the anæsthetic and an explosion took place As a result of the blast, the man, whose lungs had been full of the gas, died about $1^1/$ hours later

His widow brought an action claiming damages for negligence against the employers of the driver of the lorry, the anæsthetist, and the regional hospital board, all of whom denied these charges

Mr Justice PILCHER said that the man would have recovered had it not been for the explosion The driver of the lorry had not been negligent and hence his employers were not liable The question was whether the anæsthetist and the board had taken proper steps to guard against the risk of a spark being produced, having regard to the state of medical knowledge at the time

The Ministry of Health had for some time before 1954 interested themselves in this hazard, and had issued a number of circulars on the subject The anæsthetist had a general knowledge of static electricity and had read the circulars The senior consultant anæsthetist to the hospital board, who for these purposes represented them, was also well aware of the risk The consultant had in fact ordered anti-static rubber tubing for the breathing apparatus, which would have prevented the spark, and it had been delivered at the hospital nearly two months before the explosion, but had never been fitted, neither the anæsthetist nor the consultant viewed it with much favour, because the rubber was stiff, and for this reason it was decided to defer fitting it

As early as 1947 an authoritative textbook on anæsthesia, dealing with the risk of sparks, recommended that the relative humidity of the theatre should be not less than 60% where explosive anæsthetics were being used, and the Ministry pamphlets also made this recommendation When the explosion occurred, however, the humidity in the theatre was 25% or less This was due to a minor failure of the air-conditioning plant two days before the explosion, which could easily have been put right in that time It was clear that none of the board's servants or agents took any interest in the humidity in the theatre, although the consultant knew that dry air was particularly conducive to sparks, he took no steps to ensure that the humidity was kept up to the required percentage It was alleged against the anæsthetist that he had failed to earth the metal tube by putting his fingers on it, and that he should have realised that this was the way to eliminate the danger, although it was nowhere mentioned in the Ministry notes

His Lordship thought that the anæsthetist was entitled to assume that the humidity was correct, his first duty was to a patient who was in a bad state It would be wrong to convict him of negligence The board, however, acting through their consultant, should have realised that the only steps they could take against the risk were equipment with anti-static rubber and the institution of a system which would ensure that the air-conditioning plant kept the humidity at the necessary high level They had done neither of these things Though his Lordship was reluctant to convict them of negligence in failing to install anti-static rubber, it was impossible, after that failure, to acquit them of blame for failing to maintain the correct humidity, and the board could not escape liability

Hopley *v* British Transport Commission and Others —*Queen s Bench Division* Pilcher, *J* John Thompson, Q C , and E Brian Gibbens (Hasle woods for R Gwynne & Sons, Wellington) for the widow, Ryder Richardson, Q C , and E W Eveleigh (Gardiner & Co) for the employers, Gerald Gardiner, Q C , and Kenneth Mynett (Sharpe, Pritchard & Co for T H Waterhouse, Edgbaston) for the board James Surling, Q C , and Peter Webster (Hempsons) for the anæsthetist

GROVE HULL
Barrister-at Law

Admission of Documents to Appeal against G M C

Dr Leslie Elgar Gardiner, whose appeal to the Judicial Committee of the Privy Council against an order of the General Medical Council directing the erasure of his name from the Medical Register,[1] is expected to be heard next term, applied to the Judicial Committee for leave to adduce further evidence

Dr GARDINER, who appeared in person, pointed out that the General Medical Council and the British Medical Association were legally distinct bodies, and that in theory at any rate the former should not be influenced by the latter One important ground of his defence was that he pleaded that he had based his actions on sound examples, by following the conduct of persons whom he had considered to be of good repute and competence in his profession He would certainly have put forward before the Disciplinary Committee the activities of the British Medical Association in relation to advertising if he had known that the Committee would allow their legal representative to influence them by putting forward controversial proposed standards of an association of doctors (the B M A) overtly divided amongst themselves on these very matters The B M A 's ostensible views on advertising were deeply resented by some members of the profession He wanted to put in the new evidence because what was proposed in theory and what the B M A actually did were quite different

His petition, said Dr Gardiner, was that a number of documents—including pages from *Family Doctor*—being material published directly or indirectly by the authority of the B M A , should be admitted as new evidence, as showing by practical example, as opposed to vague theoretical recommendations, a fair cross-section of material which the B M A considered proper for doctors to publish under their names, and to address to the general public, and also as further showing the various types of advertising devices, and their usage

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[1] *Brit med J* 1933, i, 290

[1] See *Lancet*, 1960 i, 1243

At the hearing before the Disciplinary Committee he had argued that the need existed for an authoritative book on cosmetic surgery, and he wished to adduce in evidence p 392 of the *British Medical Journal* of Aug 6, 1955, to show the attitude of the B M A to this branch of surgery He also wished to base one of his grounds of appeal on the fact that the decision to erase his name was unreasonable It was very strange, concluded Dr Gardiner, that he should be the only doctor who had been found to have advertised by writing a book.

Mr PETER BOYDELL, who appeared for the General Medical Council, said that Dr Gardiner had not shown that the new evidence was not available at the hearing before the Disciplinary Committee or that it would have had, or been likely to have had, a determining influence on the decision The proposed evidence went solely to the standard to be applied by the Disciplinary Committee

Lord TUCKER, after consultation, adjourned the petition to be dealt with by the Board on the hearing of the appeal

Gardiner v General Medical Council—*Judicial Committee of the Privy Council* Lord Tucker, Lord Denning, Lord Morris of Borth-y-Gest Dec 19, 1960 Counsel and Solicitors The petitioner in person (Henry Solomon & Co), Peter Boydell (Waterhouse & Co)

CHARLES CLAYTON
Barrister at Law

Non-communication Widow's Appeal Dismissed

A butcher was boning a rump of beef when the knife slipped and caused a wound in his abdomen

A telephone call for a doctor and ambulance was sent to a cottage hospital with no resident medical staff A general practitioner, Dr R., happened to be there when the message came and at once arranged for a bed to be held at a nearby general hospital He then went to the man's place of work, made a quick examination of the wound, and had him sent to the cottage hospital where he examined the wound more carefully He concluded, wrongly as it proved, that though the deep fascia had been cut the wound had not penetrated the peritoneum, accordingly he had the wound stitched up and sent the man home, telling him that he thought it was only a surface wound, but giving him emphatic instructions to see his own doctor that evening and tell his doctor what had happened and what had been done Dr R then cancelled the bed at the general hospital

When the man's own doctor, Dr M., called that evening, abdominal pain and nausea had developed The man told Dr M that the "hospital" had said that the wound was "superficial", but Dr M., not appreciating that the hospital was a cottage hospital or the status and role of Dr R., examined his patient and diagnosed a digestive disorder During the next 36 hours the man's condition deteriorated and he died in hospital after operation. A postmortem examination disclosed that the wound had penetrated the small intestine

The widow brought proceedings for negligence against Dr R on the ground, inter alia, of failure to send a written message to or otherwise communicate directly with Dr M to report the history of the accident, the condition of the deceased, and the steps taken to investigate the extent and nature of the injury or to warn him of the possibility that the wound had penetrated to the abdominal cavity The trial judge held Dr R negligent on that ground only, namely, failure to communicate with Dr M directly by telephone or letter, and he awarded the widow £9050 damages[1] The Court of Appeal, by a majority, allowed the doctor's appeal[2] The widow appealed to the House of Lords

The House, Lord KEITH and Lord DENNING dissenting, dismissed the appeal

Lord KEITH OF AVONHOLM said that the patient fell between two stools due chiefly to failure of communication

Some communication from Dr R. to Dr M was essential. There was some communication, and the patient himself was made the medium of that communication The question was Was that communication adequate and if not was Dr R. responsible for the inadequacy and did his failure amount to negligence ? In his Lordship's view Dr R. should have foreseen that the patient's doctor, whoever he was not having all the information that he, Dr R , had, might not act as Dr R. himself would have acted, and indeed that the message which he sent would tend to mislead rather than otherwise That it did tend to mislead Dr M was clear from his evidence of how he treated the patient on the night in question A doctor who was expected to look after a patient with an abdominal wound which had already been diagnosed and treated by another doctor who had decided that the injury did not require operative or observational treatment in a hospital, should be put in possession of information as to what had been observed and done by the first doctor Otherwise the patient was deprived of the full skill, knowledge, and aid in diagnosis that the second doctor could apply to his case

His Lordship hardly regarded this as a medical question at all In his view this non-communication amounted to negligence in law, and it was scarcely in the category of professional negligence Dr R deserved great credit for the steps he took to deal with this unfortunate case, he did what he thought best in every way for the patient But he did not foresee what the results would be of sending the patient home with such an encouraging message What was foreseeable was that the patient's medical adviser would be handicapped by lack of all the information that Dr R himself had obtained The result was the delay in sending him to hospital for operation His Lordship would allow the appeal

Lord GODDARD, dismissing the appeal, said it was clear that in acting as he did Dr R was actuated firstly by his opinion that the wound was superficial but also by his view that it was necessary for the patient to be kept under observation For what other reason had he been so insistent that the patient's own doctor should be called in and advised as to what had happened and had been done ? Their Lordships knew now that unhappily Dr R 's diagnosis was wrong, but he had been acquitted of any negligence in forming that diagnosis No doctor was to be held liable for a mistake if he had used the degree of care expected of him and acted in accordance with recognised practice

His Lordship could not see that Dr R in any way misled Dr M If he had written or spoken directly to his fellow practitioner his Lordship doubted whether he would have told him more than that after observation and probing he had formed the opinion that there was no penetration, though he might have added "He needs watching", but that he might well assume Dr M would understand without being told His Lordship was not saying that Dr M must be considered negligent, it would be wrong to do so as he was no party to the action But his Lordship protested against the view that if either of these two gentlemen was not negligent the other must have been The finding of negligence against Dr R should be reversed

But his Lordship could not agree that if in the Court of Appeal Lord Justice Romer had meant to say that if a doctor charged with negligence could find two other doctors to say that they would have acted as he did that of itself entitled him to a verdict, if there was evidence the other way His Lordship preferred to think that what Lord Justice Romer meant was that if there were two recognised schools of thought on a subject one could not be negligent He would dismiss the appeal

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[1] See *Lancet* 1958 ii 1118
[2] *ibid* 1959, ii 965

Lord MORTON agreed with Lord GODDARD that the appeal should be dismissed

Lord DENNING, for allowing the appeal, said that Dr M had been misled and so fell into error Misleading information was a dangerous thing to throw about His Lordship could understand that a medical man might sometimes feel justified in giving misleading information to a patient so as not to worry him, but if he did so, he must give the true information to his relatives and, most important of all, to his own doctor who had to treat him It was the failure of Dr R to observe that rule, which his Lordship would regard as elementary, which was his mistake here Dr R had acted promptly and with the best intentions, and deserved every credit for so doing, but at the critical moment he failed

Lord HODSON, concurring with the majority in dismissing the appeal, said that it was true that the patient would be expected to pass on to his own doctor the reassuring statement that the wound was, in Dr R's opinion, superficial, but that did not cancel out the main sense of the message which was an emphatic one An object of the message must have been to guard by observation against what Dr R thought the outside chance of penetration of the peritoneal cavity having occurred

Chapman *v* Rix—*House of Lords* (Lord Keith of Avonholm, Lord Goddard, Lord Morton of Henryton Lord Denning, and Lord Hodson), Dec 21, 1960 Counsel and solicitors Roger Ormrod, Q C, and K M Willcock (Leonard Tubbs & Co), G G Baker, Q C, and P Webster (Hempsons)

M M HILL
Barrister at-Law

Parliament

Human Tissue Bill

In moving the second reading of this Bill[1] on Dec 20, Miss EDITH PITT, parliamentary secretary to the Ministry of Health, said that its provisions relating to the removal and use of parts of the body had the wholehearted support of the leading members of the medical profession During the passing of the Anatomy Bill in 1831 it had been said that though Parliament had a right to legislate for the people of this country while living it had no right to pursue people beyond the limits of the grave Some people might still have a reluctant sympathy for this view of the extent to which Parliament interferes But here certainly was an example of the House being asked with good reason to interfere for the benefit of the living and to put beyond doubt what the medical profession required for the improvement of treatment, education and research

Mr KENNETH ROBINSON paid tribute to the strides made in recent years in plastic surgery He hoped that the Bill would stimulate people to express their willingness during their lifetime for their bodies to be used in this way Miss JOAN VICKERS also welcomed the Bill but wondered whether some other title, such as Human Aid to Medical Science Bill, might not be less forbidding

Dr HORACE KING recalled that in 1952 the Corneal Grafting Bill was passed "on the nod" without debate to avoid publicity He was delighted that public opinion would now allow it to be supplanted by this wider measure Dr DICKSON MABON wondered if the Minister would justify his acceptance of the principle that the next of kin had the right of veto, in view of the large number of people who were awaiting corneal grafting operations It had been unofficially assessed that 130 people in Scotland were awaiting grafts

Mr ENOCH POWELL, the Minister of Health, said that the Bill deliberately brought the whole question into the open It was an attempt to lay clearly upon the statute-book the lawfulness of those matters concerning dead bodies which were required for medical purposes, subject to equally clearly stated stipulations and conditions He agreed that the supply of corneas was not satisfactory, probably because this part of the body had a longer history of removal for therapeutic purposes than other parts of the body The solution lay in wider public understanding—and he hoped that the debate would make its own small contribution to that—and in close relationships between the corneal grafting centres and the hospitals in the area Propaganda was undoubtedly important, and the Royal National Institute for the Blind was planning a publicity drive, in which the Minister would cooperate He agreed that the expression in the Bill "the person lawfully in possession of the body" was difficult because in law there is no property in a dead body However, he was advised that the expression would include a hospital authority in respect of a body lying in hospital, but that it would not be deemed to include the mortuary attendant of the hospital

Turning to the relatives' right to object, he said that he had deliberately left the term "any surviving relative" undefined so that it should not be necessary to inquire nicely into the degree of consanguinity, because he was convinced that more harm could be done to the purpose of the Bill by a single case in which a strongly held scruple was overridden than by any temporary loss of opportunity Where the deceased had already given his consent this could not of course be overridden by anyone The climate of opinion had changed in the past ten years and Mr Powell hoped that the public mind would open more and more both to the benefits and to the utter propriety of the processes which this Bill made lawful

Boxing

On Dec 21 Dr EDITH SUMMERSKILL asked for leave to introduce a Bill to prohibit professional boxing She said that she had powerful medical support A few skilled experts might escape, but after about fifty fights in a few years the ordinary fighter began to show unmistakable signs of deterioration No amount of medical inspection could make the sense organs less vulnerable or the bone of the temple any thicker No instrument had yet been invented which could detect the small hæmorrhages and the torn fibres of the brain which a boxer sustains in the course of a fight and which, if repeated over the years, produce the condition of punch-drunkenness When the symptoms appeared it was too late to hope that a rest would result in a cure Could anybody sensibly suggest that a screaming crowd round a boxing ring was having implanted in it the fine qualities of pluck, endurance, and restraint? Had not the time arrived when Parliament should take steps to protect our young people from the men who organise these displays on highly profitable business lines?

Lieut-Colonel W H BROMLEY-DAVENPORT said that the British Boxing Board of Control, of which he was a member, had authority to issue licences, at its absolute discretion, to all persons connected in any way with professional boxing Every applicant for a boxer's licence had a comprehensive medical examination, and if he was fit he was granted a licence Boxers must be examined before and after every contest, and if a boxer was knocked out he must be medically examined before he even contracted to box again Unless a boxer got a certificate of absolute fitness from his area medical officer his licence was suspended until he was fit, and if necessary it was withdrawn altogether In the event of a knock-out, all officials have a complete knowledge of first-aid All the evidence showed that recovery from a reflex knock-out was complete and almost immediate and that, with rest and abstention from boxing, complete recovery also took place after a concussion knock-out It was unfounded speculation to say that the evil effects might show themselves years later Members of the Board had long practical experience in boxing and were assisted by some of the best brains in the medical profession As for the medical profession itself, every year the hospitals held their own boxing championships, and these were attended by all branches of the medical profession Would medical men support these shows if they thought that they were harmful to others?

The motion was lost by 120 to 17

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[1] See *Lancet*, Dec 17, 1960, p 1354

QUESTION TIME

Drug Prices

Mr KENNETH ROBINSON asked the Minister of Health, arising from the new drug-price agreement, of how many drugs the price would be directly negotiated, and what provision there was for the list to be expanded, whether the export price criterion remained the average export price, and whether the definition of new drugs lay within his control —Mr ENOCH POWELL replied Negotiations will be opened at once on the prices of a few widely used drugs which together account for nearly half the value of those satisfying the export price criterion Other drugs in large demand by the Health Service will be considered from time to time The export price criterion remains the weighted average export price New drugs in this context are defined in the scheme

Fatal Overdose

Mr E L GARDNER asked the Minister what action had been taken in the case of the doctor responsible for prescribing an overdose of xylocaine, equivalent to almost three times the normal dose, for a child 4 years of age who died in St Andrew's Hospital, Billericay, as a result of the overdose given to relieve the pain of a fractured wrist —Mr POWELL replied A claim against the doctor by the father has been made and settled The doctor had already resigned before the accident and his resignation took effect shortly after As a result of the accident, fresh guidance on local analgesics by the group medical advisory committee has been brought to the notice of all medical staff in the group Mr GARDNER May I ask whether the doctor who made this elementary and fatal mistake will be given refresher training in the safe use of drugs like xylocaine before he is allowed to prescribe them again? Can the Minister say whether any hospital to which this doctor may be appointed will be given notice of his present inexperience? Mr POWELL I have not got the information, but it is the duty of boards and committees to acquaint themselves with the qualifications and record of anybody whom they consider appointing Mr ROBINSON Does not the Minister appreciate that it is extremely difficult for boards and committees to acquaint themselves with the record of people they are appointing and that matters of this kind are very seldom referred to in references from previous employers? Mr POWELL But it is the duty of these authorities to assure themselves that the references they obtain are adequate to ensure that they are aware of the qualifications and the records of the people they are appointing

R C P's New Building

Mr ROBINSON asked the Minister of Housing and Local Government and Minister for Welsh Affairs if he was now prepared to authorise the London County Council to grant planning permission for the new headquarters of the Royal College of Physicians on the east side of Regent's Park Mr HENRY BROOKE replied Yes Sir Mr ROBINSON May I ask the Minister to accept the congratulations of hon Members on this side of the House for approving a design which is brilliant and imaginative and blends very well with its surroundings?

Smallpox in Nyasaland

Earl WINTERTON asked the Government whether the smallpox epidemic in Nyasaland had now abated what was the estimated number of the inhabitants of Nyasaland who had been vaccinated during the present year and whether any action was possible under the laws of Nyasaland to prosecute those persons who, by intimidation, had attempted to persuade the inhabitants of Nyasaland not to be vaccinated —The Earl of PERTH, Minister of State for Colonial Affairs, replied My Lords, health is a responsibility of the Federal Government, but I am informed that the epidemic has not yet subsided The total number vaccinated is over 480,000 When intimidation involves threats of unlawful action such as violence to persons or property or is carried out by unlawful means, including unlawful conspiracy, the laws of Nyasaland provide for action to be taken against the offenders In two instances where medical teams have been hindered by physical intimidation the authorities brought forward cases for trial One has resulted in the conviction of the principal offenders and the other is shortly to be heard

Surgeon for St Helena

Mr CLEDWYN HUGHES asked the Secretary of State for the Colonies what salary was paid to the senior medical officer for St Helena —Mr IAIN MACLEOD replied Up to £2500 a year depending on qualifications and experience Mr HUGHES Are there not difficulties in getting an experienced surgeon for this remote island? Has not the salary something to do with it? Will the Minister consider giving a higher starting salary to doctors who go there? Mr MACLEOD I think that the salary has something to do with it It was less than half this figure about two or three years ago I believe that it is as a result of the offer of this amount that we have attracted a suitable candidate I hope that he will go to the Colony early next year

Mr HUGHES asked the Secretary of State whether he would give details of the arrangements now in force for a surgeon to visit St Helena, and what provisions existed for dealing with an emergency case needing immediate surgical treatment —Mr MACLEOD replied Arrangements are being made by the governor for a surgeon to visit St Helena as soon as practicable While recognising that the present situation cannot be accepted for an indefinite period I am satisfied that the medical officer in St Helena has sufficient experience of surgery to enable him to deal with such emergencies as might arise Mr HUGHES Can the Minister say how long it takes an experienced surgeon to get to St Helena? Mr MACLEOD I suppose it depends on how he travels Offhand I do not know the answer, but I will find out Mr HUGHES Is it not the case that he takes four or five days to get there? Mr MACLEOD That might well be so The surgeon that I have in mind is in practice at Cape Town

Psychiatric Qualifications of Prison Medical Officers

Mr LEOPOLD ABSE asked the Home Secretary whether he was aware that prison medical officers lacking a recognised psychiatric diploma were regularly submitting reports on the sanity of accused person to the courts and what steps he was taking to increase the number of prison medical officers who hold a diploma in psychological medicine —Mr R A BUTLER replied Few prison medical officers who submit reports to court on the mental condition of inmates possess a recognised psychiatric diploma though all have experience in the diagnosis of mental disorder and the majority are approved by local health authorities for the purposes of section 28 of the Mental Health Act 1959 In recruiting prison medical officers, weight is given to the possession of a diploma in psychological medicine, and encouragement is given to medical officers in post to take the diploma wherever possible

Medical Examination of Accused Persons

Mr ABSE asked the Home Secretary whether he was aware that persons in custody charged with murder were being compelled to submit to psychiatric examinations by prison medical officers and that the facts so obtained were supplied to the Director of Public Prosecutions, and whether he would give instructions that no psychiatric examination of an accused person charged with murder should take place and no report be given to the Director of Public Prosecutions, except with the consent of the accused or their legal advisers —Mr R A BUTLER It has for long been the established practice for a report on the mental condition of any prisoner charged with murder to be furnished by the prison medical officer to the court through the Director of Public Prosecutions, who supplies a copy to the defence The Royal Commission on Capital Punishment approved this practice but recommended that such prisoners should in future be examined by an independent psychiatrist of standing as well as by an experienced member of the prison medical service The Government accepted this recommendation I see no reason to disturb the existing arrangements which have been generally accepted as being necessary and desirable in the interests of justice

Obituary

ERNEST FREDERICK FINCH

Kt, M D, M S Lond, Hon D Sc Sheff, F R C S, Hon F R C S I

Sir Ernest Finch, a former professor of surgery in the University of Sheffield and vice-president of the Royal College of Surgeons of England, died on Dec 16 at the age of 76

He began his medical studies at Sheffield in 1901 at a time when the College had not yet attained university status and its medical students graduated in London He accordingly graduated M B Lond in 1906, but after Sheffield University was granted its charter he was admitted to the M B, CH B Sheffield degrees ad eundem After holding an appointment in the physiology department at Sheffield he took the M D Lond in 1909 He had already chosen surgery as his specialty, and in 1911 he took the F R C S and in 1913 the M S Lond Meanwhile his long association with the Royal Infirmary had already begun with his appointment as house-surgeon in 1907 In due course he became resident surgical officer and surgical registrar, and in 1912 he was elected to the honorary staff In the 1914–18 war he served in France with the 3rd West Riding Field Ambulance (T A) and later at the 3rd Northern General Hospital in Sheffield with the rank of major

Walter Stoneman

On demobilisation Finch returned to his busy hospital and private practice and to his many other surgical interests and duties Important among these was his work at the medical school, where he was for many years lecturer in clinical surgery In 1934 he was appointed to the chair of surgery After he retired from his chair and appointments in 1944 he gave increasingly of his time and energy to the Royal College of Surgeons

He was elected to the council in 1940, and he served as a member until 1956, and as a vice-president in 1953 He was successively Bradshaw lecturer, Vicary lecturer, and Hunterian orator, and was for ten years a member of the court of examiners He was an early member of the Moynihan Chirurgical Club, of which he was secretary from 1926 to 1947, and later president He was also president of the Association of Surgeons of Great Britain and Ireland from 1939 to 1942

He was created knight in 1951 The honorary degree of D SC Sheff was conferred on him in 1953 and the honorary fellowship of the Irish college in 1959 In 1946 he was elected a member of the Sheffield Town Trust

F W H writes

" The Sheffield Medical School, founded on firm principles largely laid down by the late Sir Arthur Hall, owes its rapid development and present reputation in great measure to the wise guidance and gentle diplomacy of Ernest Finch He had a clear picture of how a medical student should be taught and, especially while professor of surgery, he spared no effort to establish the type of curriculum and examination which he believed to be right He was a great friend of all young surgeons, doing all in his power to help and advise them, not only as to their careers and in professional matters, but in any adversity He will be remembered as a great surgeon, a great doctor, but above all as a good and kind man "

T B M writes

" Ernest Finch was a Sheffield man who by his knowledge and charm of manner found many friends and a great place in a wide surgical world as examiner, member of council, and later vice-president of the Royal College of Surgeons of England

" For many years the genial and efficient secretary of the Moynihan Surgical Club, he, and through him the club, became widely known in many Continental surgical clinics He was greatly beloved and esteemed by all who knew him—many went to him for help and advice and he never failed them He was tireless in his work for the students and for the welfare of the nursing staff, who were all devoted to him "

H P found Sir Ernest's leadership and friendship " manifest in every sphere of his unceasing activities "

" In Sheffield [he continues] Ernest Finch had become the doyen of its medical world, in the Royal College of Surgeons his long service on the council had been crowned by his memorable scholarly Hunterian oration, and in the affairs of the Association of Surgeons and the *British Journal of Surgery* his wisdom and shrewdness were invaluable To young surgeons in Sheffield and elsewhere, he was a true ' father in surgery ', they saw him as a man devoid of all envy To his contemporaries, his friendship was always a source of comfort and inspiration During the last fourteen years we saw him facing illness with indomitable courage And when he knew that his end was near, he continued to show to those around him that æquanimitas which was one of his most lovable characteristics He welcomed with quiet dignity the honours which came to him, and indeed they might have been more But what he cherished above all was the affection of his many friends, young and old "

In 1912 Sir Ernest married Miss Mary Ainsworth, who survives him with their son

ROBERT LIGHTBODY GALLOWAY

M B Edin, F R C S E

Mr R L Galloway, medical director of the West Middlesex Hospital, London, died in Edinburgh on Dec 3

He was born in Edinburgh in 1895, and after attending Daniel Stewart's College he took up his medical studies at the university, graduating in 1919 and proceeding to the F R C S E six years later He was from his earliest days attracted to surgery, and, after working under such men as Alexander Miles, Prof F M Caird, and Sir Harold Stiles, he was appointed resident surgical officer at the Manchester Royal Infirmary and Salford Royal Hospital During these appointments he developed a surgical dexterity and speed which earned for him wherever he operated the admiration and respect of his colleagues

In the middle '20s he was appointed surgeon to the North Middlesex Hospital, where he considerably enhanced the prestige of this expanding hospital With the advent of the 1939–45 war he was transferred to Chase Farm Hospital, where he not only maintained a busy surgical unit but also largely contributed to the administration involved in building up and running a large general hospital as part of the Emergency Medical Service His organising ability was so evident that when the post of medical director at the West Middlesex Hospital fell vacant after the war he was invited to fill it He was here largely responsible for coordinating and supervising the post-war building and redevelopment programmes which are still in progress Until shortly before his retirement last March he remained an active surgeon, and regularly carried out long operating sessions

He employed his gift of manual dexterity in fields outside that of general surgery He maintained an engineering workshop, and not only worked in silver and other metals but also egularly serviced surgical instruments in daily use in the hospital. In his earlier years he was keenly interested in motor-cycle racing and sometimes surprised colleagues who were unaware of this hobby by appearing as headline news in the sporting sections of the daily press

A colleague writes

"Despite his high reputation as a surgeon, administrator, and sportsman Mr Galloway had essentially a retiring, modest nature. He was readily agreeable to any reasonable request made to him, but if he felt it necessary to speak strongly he would make his views known in an emphatic manner He evoked the admiration both of his medical and nursing colleagues, and all members of the hospital staff knew they would always find in him a sympathetic listener and a sound adviser He brought a touch of humanity into his administrative work which was much appreciated by all who came in contact with him. In Mr Galloway's untimely death we have lost a wise counsellor and a loyal friend."

Another colleague adds

"There can have been few British surgeons in the second quarter of this century who crowded so much work into their life as R. L. G At the North Middlesex and later at Chase Farm he got through an incredible volume of general surgery, with great skill speed, and gusto In the 30s at the North Middlesex it was nothing for 'Robbie' to finish a list of ten cases by lunch-time and on a busy take-in to operate on another dozen emergencies, finishing his day at 3 A.M. by giving a lift home to the no-longer-anxious relatives of his last case These emergencies would be of all sorts—provided they were surgical it did not matter appendices obstructions, fractures, mastoids head injuries—Robbie took them all in his stride, deftly quickly, with no movement wasted. He never grumbled at there being too much to do, but he was the first to admit that he would have liked more time and facilities to collect and consider his work—provided there was no fall off in the amount. He was so busy *doing* that he had no time and indeed little use for writing He might well have inspired Bernard Shaw to say 'He who can, does he who cannot teaches' Curiously enough, however on the two or three occasions when he was persuaded to report his surgical experiences before the Section of Surgery of the Royal Society of Medicine or the Middlesex Medical Society, his contributions were notably good. His papers on perforated peptic ulcers and on thymectomy for myasthenia gravis come easily to mind—though he himself regarded them almost as a penance

"Robbie looked every inch the surgeon doing his ward-rounds in his bespoke, button-up-collar, white coat—perhaps his only foible apart from fast cars and home-made motor-bikes For years he spent his summer holidays driving his motor-bike as far as he could to some wild corner of Europe and back home again in a fortnight He liked his fellow men and loved his job"

Mr Galloway is survived by his wife and by a son and a daughter

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Appointments

[illegible], HORACE, M.B. Sheff., D.P.H. M.O. and school M.O. Chesterfield

[illegible], JOAN M., M.B. Manc. assistant divisional M.O. Whitworth and [illegible] area Lancashire.

DALTON, G. A., M.B. Birm., F.R.C.S., D.L.O. part-time consultant E.N.T. surgeon United Birmingham Hospitals

DUNBAR, THOMAS, M.D. Glasg. consultant psychiatrist and physician-superintendent Harwood Mental Hospital Shotts Lanarkshire.

[illegible], D. E., M.B. Madras, D.T.M. & H., D.P.H. senior administrative M.O. for the mental-health service, West Riding of Yorkshire.

KYLE, JAMES, M.CH. Belf., F.R.C.S. part-time consultant general surgeon Aberdeen General Hospitals

URQUHART, MARGARET C., M.B. Glasg. assistant M.O.H. and school M.O. Derbyshire.

[illegible], F. G., CH.M. Leeds, F.R.C.S. consultant general surgeon, General Infirmary at Leeds and Leeds and Wakefield hospitals

[illegible], MARY M., M.B. Glasg. part-time assistant M.O.H. and school M.O., Derbyshire.

Colonial Appointments

MCCARROLL, L. J., M.B. Edin. M.O. Bahamas

ORR, C. J. B., M.B. Dubl., M.R.C.O.G. M.O. Bahamas

[illegible], P. H., M.B. Leeds M.O. North Borneo

[illegible], M.D. Bristol M.O., Bahamas

[illegible] L. M., M.B., D.T.M. & H., D.P.H. M.O. Hong Kong

[illegible], J. R. R., M.R.C.S., D.P.H. senior M.O. Kenya

Notes and News

NEW SALARY SCALES FOR BIOCHEMISTS AND PHYSICISTS

THE following revised scales for full-time hospital biochemists and physicists who are not medically qualified have been accepted by the Ministry of Health

Basic grade—Probationary period £650 x £25 (2)–£700 x £30 (4)–£820 x £35 (3)–£925 Post-probationary period £925 x £35 (2)–£995 x £40 (3)–£1115 x £35–£1150 *Senior grade*—£1250 x £50–£1300 x £55 (3)–£1465 by £60 (3)–£1645 x £55–£1700 *Principal grade*—£1750 x £70 (3)–£1960 x £80–£2040 x £85–£2125 *Top grade*—at least £2250 x £75 (2) x £100 (2)

Employing authorities are also given wider discretion to award higher starting pay to probationers who have an honours degree or postgraduate experience. The new scales will come into operation on Feb 1

FILM ON SUBNORMAL CHILDREN

THE mentally subnormal child, like everyone else responds to his environment. He develops less well, for example, in a crowded impersonal institution than in an intimate attentive family circle A systematic study of such influences on the development of skills and behaviour lately conducted by Dr Jack Tizard with the help of the Fountain Hospital has now been admirably recorded on film [1] In the 'Brooklands experiment" sixteen children aged 4–10, carefully matched with controls, were boarded out of the Fountain Hospital to a pleasant country house where they were brought up in 'family" groups and educated on nursery-school principles according to their mental age This life is vividly shown in the film with illustrations of progress made over two years, though the formal control experimental data are not given Unhappily, staff and facilities of this order are available to few of the 9000 or so mentally handicapped children in our hospitals But hope of any kind shines particularly brightly in this rather unrewarding sphere of work, and anyone connected with it will find the film stimulating and important

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University of Cambridge

On Dec 10 the degrees of M.B., B.CHIR. were conferred on H. M. James (by proxy) and J. A. Dyde

University of Bristol

At recent examinations for the degrees of M.B., CH.B. the following were successful

Linus Nwachukwu [illegible], Frances N. B[illegible], Belinda R. Davies, [illegible] Olarinka [illegible], D. D. Kennedy, W. T. Morris, J. J. Nichols, G. H. Robb, Hassan [illegible], R. M. Sykes

University of Manchester

At recent examinations the following were successful

M.D.—H. W. Ashworth, E. G. D[illegible], T. G. Ram[illegible], C. F. H. Vickers

M.B., Ch.B.—David Ashcroft, Peter Asquith, A. J. Bar[illegible], N. D. B[illegible], A. G. Brown, S. G. W. Gough, D. E. Hamilton, C. A. Hope, D. G. Johnson, Hazel I. Ke[illegible], I. C. McInnes, Philip Mills, P. F. Norman, Linda M. Tye, Alan Westerman, R. S. Whitaker

D.P.H.—Angela [illegible] M. [illegible], Lydia McMurdo, D. S. Ross, [illegible] S[illegible]

University of Durham

Dr L. G. Kiloh has been appointed reader in psychological medicine and Mr P. C. G. Isaac reader in public health engineering

University of Sheffield

Dr Alan Usher has been appointed lecturer in forensic medicine and Dr Harold Merskey lecturer in psychiatry

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[1] Mentally Handicapped Children Growing up. The Brooklands Experiment. 16 mm., sound, black and white, 21 minutes. Produced by Realist Film Unit Ltd. Obtainable from the National Society for Mentally Handicapped Children, 125 High Holborn, London W.C.1

University of Leeds

At recent examinations the following were successful

M D—R H P Fernandez

M B , Ch B—David Hopwood (second class honours) A S Abraham Nicholas Benn Elizabeth K Bullock D A Carter, D E Clark, G A Collingwood, Dorothy M Eaton Kathleen M Fearn, I W Geere, Frank Hainsworth, S M Haworth, D S Hinson, Anne Johnson, D H Kenward, Margaret Lambson, Brian Livesley, Sylvia E Lyth, D L Matthews, A S Meltzer, Jennifer B Mencher, D W Miles, Mary V W Murtagh, M J Ognall, Mary W R Parsison, S D Platts, Jean Nöel Poilly, Anne Randles, C C Robertson, T H Rosengarten, P R Scotter A E Todd, Terence Vickers D J Wadsworth, J K Wales W D Walls Joan A Watson, E J Williams, M E Wilson, Marjorie Yeomans

University of Liverpool

On Dec 16 the following degrees were conferred

M D—E C Edwards, T S Eimerl, Eva Gallagher, W B Jennett, C R Kay, W W Littler, J M Nichols Alan Patterson, John Stanley Robinson David Sykes

M Ch Orth—Niranjan Das Aggarwal J G Allman, Donovon Mark Amerasinghe Ali Muhammad Yakub Ansari, F J Harvey, Charles Malkin J G Sallis, F F Silk, H C Van Der Post

M B B Ch—J J Aitken, H B Asafu Adjaye Ruth M Berry, H J Bradley, M C Donaghy, Mai Edwards, Michael Gornall, A G Hayes, Caroline N Jones N E Lipkin, R F Longdin B C Longstaffe N A Lycett, T T Westhead J A Whittaker, J N Whittaker, M W G Wren

At recent examinations for the D T M & H the following were successful

B O Amure S S Apte W A K Aruwa, H Bart-Plange P G Comer, W E Cooper D Dean V De Sario Eileen T Duffy E U Essien, J C Fluth M T Ganpule, K M Gothe T S C Lim M F Luke, R C Lutz J J McNair G S Murty, S A A Ogunlusi, J C Okoye, E Onori, R O Parnis, D Felix Richards, N S Salem J A Smith, D Sonakul, I A Susman K Thakur, A J Whitley

University of Edinburgh

On Dec 16 the following degrees and diplomas were conferred

M D—J A L Gorringe *T J McNair, *H A Reid (commended for thesis) R L Lyon

Ph D (*in the faculty of medicine*)—Archana Basu, Marcus Jacobson

M B Ch B—W R Bonne, T O Brackett Barbara Brumby C F Butler J R V Carlisle Margaret J Chapman Adrian Clancy J O Djan J B P Ferguson H W Hamilton R J Inglis, Mohamed Nawaz Kaleel, T M Kennedy, Robert Kerr, Jane K S Kirkwood Derek Lewis Michael McCafferty Henry Mercer Ricketts, W A Shafto G W Somerville M W Watkins, Sandra C Wedderspoon I A G Weston

D.P H—Ti Yuen Lee Pijush Kanti Nag Elizabeth M Watson

D M R D—W C Hartley, A A Marr, E N C Milne, Patricia Morley

D M R T—J R Brown, G L Ritchie, Agnes R Russell

D P M—H C Bethune, J R B Saxby

* In absentia

Royal College of Physicians of London

Dr Clifford Hoyle will give a Marc Daniels lecture on Thursday, Jan 12 He will speak on the prognosis of pulmonary sarcoidosis Dr D A Pond will give the Goulstonian lectures on Tuesday and Thursday, Jan 17 and 19 His subject will be psychiatric aspects of epileptic, brain-damaged children The lectures will be given at 5 P M at the college, Pall Mall East, S W 1

Royal College of Surgeons of Edinburgh

At a meeting of the college on Oct 16, with Prof John Bruce, the president in the chair, the following were admitted to the fellowship

Fayik Rifat Abdi, Venkataramanan Balasundaram G S Banwell, Rathevos Martyr Carapetian, M H Carr, A J M Cathro, Jagdish Kumar Chaudhry, Soo Huat Choo Mahmud Ali Chowdhury Nagendra Nath Roy Chowdhury Mriganka Mohan Das Prafulla Bhagubhai Desai, Monoranjan Duari, S R Duke M D FitzGerald R M Gray, R W Goonewardene C H Hodge J D A Henshaw, A G Hutchison B J H Insull Sugan Chandra Jain Sohan Lal Johari Mathew John Hasmukh Harilal Kamdar C S Karmody J N Kille E O G Kirwan, P J Kleyn J H Lawrie J N Livingstone C J H Logan, J D C Macdiarmid T S Mann L S Marriott Bimalendu Mukherjee, Padmanabhan Narayanan Unni Chuan-Wai Ng Narayan Vithal Nimbkar Ibiyemi Ogunyemi Ballambettu Yogish Pai, Natwarlal Gangjibhai Patel Harish Chandra Puri Gopal Ramaswami, Arun Bhaskerrao Rindani Jawaharlal Tribhovandas Shah Thamotherampillai Nadarajah Shanmugalingam G R Sharp Pundalika Mangalpady Shenoi, N D J Smith Ebrahim Gulamhussein Soorma, W A Souter, Jamsheed Cooverji Taraporvala, J A W T Wells Pannianpalli Krishna Raghava Warrier C R Wilson, R D Wolff

British Association of Plastic Surgeons

The following officers have been appointed for 1961

President, Air Commodore G H Morley, immediate past president, Mr P H Jayes, hon treasurer, Mr R P Osborne, hon editor, Mr A B Wallace, hon secretary, Mr John Watson, members of council, Mr R J V Battle, Mr C R McLaughlin, Mr I F K Muir, Mr E W Peet, Mr J S Tough, overseas representative on council, Mr N A M Petersen (South Africa)

Order of St John of Jerusalem

The Queen has sanctioned the following promotions in, and appointments to, this order

As Knights—T D W Fryer, M B , Sir Harry Chapman Sinderson, K B E , C M G , M V O , J A Carman, M D , E M Dearn, M B , Colonel Sir William Coates, K C B , C B E , V D , T D , F R C S

As Commanders (Brothers)—D J Turnbull, M R C S , J T Watkins, M B , Air Commodore G H Morley, O B E , Q H S , F R C S

As Officers—R L Brown M B , C N Burnham Slipper, T D , M R C S , E T Weekley, M R C S , E B Figueiredo, M B , H E Hobbs, F R C S , O A Tomlinson, L R C P I , William John Gerard Drake Lee, M B

Society of Apothecaries of London

The following diplomas have been granted

M M S A—R M Burton, F L W Collings

L M S S A—J J Aitken W K Blenkinsopp, J Brown, M H Chu, R N Drepaul, H M Gillespie, F D Habib, C S Jayakumar, J M Lilwall, R Marris, B R Middleton G Z Shenouda, P Singh I G Strang, J Swallow, A Thomas, I A Tuncer, C R S M Wynne Roberts

Institute of Neurology

On Thursday, Jan 5, at 5 P M , at the institute, Queen Square, London, W C 1, Dr Carl Pearson of the University of California will give a lecture on biochemical studies in muscle disease

Royal Society of Medicine

On Wednesday, Jan 4, at 8 P M , in the section of surgery Mr Hugh Harley, Mr L D Abrams, Mr Ivor Lewis, and Mr Ashton Miller will open a discussion on non-penetrating injuries of the chest and abdomen On Thursday, Jan 5, at 8 P M , in the section of neurology there will be a discussion on steroid therapy in neurological disease The speakers will be Prof I E Bush, Dr Stanley Graveson, and Dr Henry Miller On Friday, Jan 6, at 5 30 P M , in the section of anæsthetics Dr J J L Ablett will read a paper on the management of tetanus All meetings will be held in the society's house, 1, Wimpole Street, London, W 1

King Edward Medical College, Lahore

At the centenary celebrations of this college last month, presided over by the President of Pakistan, the University of the Punjab conferred the honorary degree of doctor of laws on Major-General Sir Alexander Biggam, former director of the Postgraduate Medical Board, Edinburgh, Lieut -General Sir Alexander Drummond, director-general, Army Medical Services, Mr Charles Wells, professor of surgery in the University of Liverpool, Lieut -General Wajid Ali Burki, Minister for Health, Labour, and Social Welfare, Pakistan, and (posthumously) Lieut -Colonel Ilahi Bakhsh, formerly principal of King Edward Medical College, Lahore

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Mr T Holmes Sellors is attending as a guest the meeting of the Indian Association of Surgeons in Poona from Dec 27 to 31, and continuing on a lecture tour in some of the major centres, under the auspices of the British Council, during January

Dr M I F Drury has been appointed to deliver the Graves lecture of the Royal Academy of Medicine in Ireland and the Medical Research Council of Ireland in 1961

At a meeting of the Medical Electronics Discussion Group on Friday, Jan 6, at 6 P M , at the Institute of Electrical Engineers, Savoy Place, London, W C 2, there will be a discussion on image intensification techniques in radiology

The Ministry of Power has published its digest of statistics of pneumoconiosis in the mining and quarrying industries for 1959 Copies may be had from H M Stationery Office (3s 6d)

A semipermanent exhibition will be held at the Institute of Dermatology, Lisle Street, London, W C 2, from Jan 9 to 27, by Mr R J Lunnon on direct ultraviolet photography of the skin

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CORRIGENDUM *Arterial Replacement and Reconstruction*—In this article by Mr D J Tibbs (Dec 17, p 1313) the word 'amputation' should have appeared in fig 4 opposite the second case in which a 'Dacron' by-pass procedure was undertaken on account of rest pain or gangrene in addition to claudication

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PUBLISHED by the PROPRIETORS, THE LANCET LIMITED, 7 Adam Street, Adelphi in the County of London
Printed by HAZELL, WATSON & VINEY LTD , Slough and Aylesbury—Saturday, March 11, 1961
PRINTED IN GREAT BRITAIN—Entered as Second Class at the New York, U S A , Office